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**Knowledge Synthesis:
Identifying Optimal Treatment Approaches for People with Multimorbidity in Ontario**

10 April 2013

McMaster Health Forum

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Merit review

The knowledge synthesis was reviewed by a small number of policymakers, stakeholders and/or researchers in order to ensure its scientific rigour and system relevance.

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KEY MESSAGES

Problem of multimorbidity

- Efforts to address the challenges associated with providing care for people with multimorbidity will need to consider several features of the problem, including the:
 - growing prevalence of multimorbidity coupled with the fact that prevalence grows steadily with age, meaning that the problem will continue to grow with an aging population;
 - complexity of living with and treating multimorbidity given that the health risks associated with multiple conditions are numerous and varied, and treatment is made difficult given uncertainties about the benefits and harms of simultaneous treatments (e.g., by following multiple disease-specific treatment guidelines that may provide conflicting or impractical recommendations);
 - heavy burden faced by patients with multimorbidity and their caregivers (e.g., people with multimorbidity have greater self-care needs and often rely on informal/family caregivers);
 - impact of multimorbidity on healthcare utilization and costs given that adults with multimorbidity are significant users of healthcare services and account for more than two-thirds of healthcare costs; and
 - fragmentation of current programs and treatment strategies for patients with multimorbidity that results in recurring challenges for people to get the care they need.

Addressing multimorbidity

- Understanding health risks for people with multimorbidity
 - From the three systematic reviews and five observational studies we identified, the main consequences of multimorbidity were functional impairment, poor quality of life, high healthcare utilization, high out-of-pocket costs and increased burden on the patient for their care. There was inconsistent evidence regarding whether multimorbidity disproportionately increases the risk of mortality. One recent medium-quality systematic review revealed that mental–physical multimorbidity is common in long-term care residents. Another systematic review found that certain combinations of chronic conditions (e.g., chronic respiratory disease, congestive heart failure and diabetes) present a greater risk for physical decline than other combinations. A third systematic review found a large social network to be a protective factor for the consequences of multimorbidity.
- Characterizing programs and models for treating people with multimorbidity
 - A recent high-quality review found that interventions focusing on specific risk factors or impairments might be more effective than organizational and patient-oriented interventions which had mixed effects on health outcomes. Another recent medium-quality review found inconsistent evidence for the effectiveness of comprehensive care programs based on components of the Chronic Care Model, but their effects appeared comparable to or more positive than those of usual care. A third recent and high-quality review found that both computerized decision support and pharmaceutical care interventions reduced inappropriate medication use. Several primary studies identified a range of promising interventions including nurse-led interventions, pharmacist-led shared medical appointments, guided care teams, and patient-centred, team-based collaborative care management.
- Identifying promising guidelines for treating people with multimorbidity and models for developing such guidelines
 - We identified several overviews of the applicability of existing guidelines to multimorbidity (each found few or no guidelines addressing treatment for multimorbidity), a small number of guidelines that provide implications or recommendations for treatment (but none that focused exclusively on multimorbidity), examples of sets of principles that had been developed for the creation of multimorbidity guidelines (e.g., for older adults with multimorbidity) and examples of recent initiatives that suggest a strong interest in the development of guidelines for treating multimorbidity.

Discussion

- There is a need to better understand the complex array of both risk and protective factors for multimorbidity or multimorbidity sequelae (e.g., genetic, biological, environmental and psychosocial factors) and to build on promising programs, models and guidelines to inform the development of treatment strategies for people with multimorbidity.
- Given the complex needs of people living with multimorbidity, it is generally expected that promising programs and models are likely to be complex and multifaceted.

INTRODUCTION

Multimorbidity is part of the daily life of a growing number of Ontarians who must manage multiple chronic conditions. As Fortin et al. observed, “patients with multiple conditions are the rule rather than the exception in primary care.”(2)

Multimorbidity not only has a significant impact on healthcare utilization and costs, but it is expected to affect quality of life, ability to work, employability, disability, process of care and mortality.(3) Despite the burden of multimorbidity, patients often receive care that is “fragmented, incomplete, inefficient, and ineffective.”(3) Thus, there have been growing calls for changes to health systems and clinical decision-making processes to more effectively and efficiently provide the complex care required by those with multimorbidity.(4;5)

In 2007, the Ontario Ministry of Health and Long-Term Care (MOHLTC) developed a chronic disease management care framework.(6) While the framework emphasizes interdisciplinary and integrated care teams, it does not provide clear direction on the role of primary care to support patients with multimorbidity. As the burden of chronic disease continues to grow, the health system in Ontario will need to adapt from being focused more on acute care to an integrated system that supports the complex challenges faced by people living with chronic disease and, in particular, those with multimorbidity.

This knowledge synthesis was designed to support the actions of those involved with addressing the challenges associated with providing care for people with multimorbidity. The knowledge synthesis first provides an overview of key features of the problem related to multimorbidity, which include the growing prevalence of multimorbidity, the complexity of living with and treating multimorbidity, the heavy burden on patients and caregivers, the impact on healthcare utilization and costs, and the fragmentation of programs and treatment strategies. Second, we present findings from the synthesis where our objectives were to identify:

1. research evidence examining the health risks, risk factors and protective factors faced by people with multimorbidity;
2. programs and models (at both the system and guideline level) for treating patients with multimorbidity that support efficient, patient-centred care as well as health promotion, prevention and early detection in different settings (e.g., primary healthcare, acute care and long-term care); and
3. promising guidelines and models for treating people with multimorbidity.

Box 1: Background to the knowledge synthesis

This knowledge synthesis mobilizes both global and local research evidence about a problem and possible approaches to address it. Whenever possible, the knowledge synthesis summarizes research evidence drawn from systematic reviews of the research literature, clinical guidelines and single research studies. A systematic review is a summary of studies addressing a clearly formulated question that uses systematic and explicit methods to identify, select and appraise research studies, and to synthesize data from the included studies. Within this scope, the knowledge synthesis is focused only on the best available evidence and does not contain recommendations, which would have required the authors of the synthesis to make judgments based on their personal values and preferences, and which could pre-empt important deliberations about whose values and preferences matter in making such judgments.

The preparation of the knowledge synthesis involved five steps:

- 1) convening a Steering Committee comprised of representatives from the partner organization, content experts and the McMaster Health Forum;
- 2) developing and refining the terms of reference for the knowledge synthesis, particularly the framing of the problem, the scope of the synthesis and the methodology, in consultation with the Steering Committee and a number of key informants;
- 3) identifying, selecting, appraising and synthesizing relevant research evidence;
- 4) drafting the knowledge synthesis in such a way as to present concisely and in accessible language the global and local research evidence; and
- 5) finalizing the knowledge synthesis based on the input of several merit reviewers.

Lastly a discussion of the results is provided to highlight the key findings, implications, and the strengths and limitations of the synthesis. Within this scope, the knowledge synthesis is focused only on the best available evidence and does not contain recommendations.

This knowledge synthesis draws on several terms and concepts including chronic disease, approaches to managing chronic disease, comorbidity and multimorbidity. In general, chronic diseases refer to “health problems that require ongoing management over a period of years or decades.”(7) Integrated chronic disease management can be defined as the prevention and management of chronic disease that “aims to reduce overall risk in high-risk individuals and provide appropriate care by facilitating early case finding through affordable strategies and technologies, and equitable and good quality health care for major chronic diseases”. (8) An extensively studied example of an integrated approach is the Chronic Care Model which Boyd et al. (2010) highlight as a promising framework to organize the essential elements of a health system providing optimal care for people with multimorbidity.(3) The Chronic Care Model combines the following six features:

- self-management support (i.e., empowering and preparing patients to manage their health and healthcare);
- decision support (i.e., promoting clinical care that is consistent with scientific evidence and patient preferences through, for example, embedding evidence-based guidelines as well as related patient decision aids into daily clinical practice, and supporting their implementation through continuing professional development);
- delivery system design (i.e., organizing programs and services to assure the proactive, culturally sensitive delivery of effective, efficient clinical care and self-management support by healthcare teams);
- clinical information systems (i.e., organizing patient and population data to facilitate more efficient care through, for example, an electronic health record that provides reminders for providers and patients and monitors the performance of healthcare teams and the system in which they work);
- health system changes (i.e., creating a culture, organization and mechanisms that promote safe, high quality care, which can include visibly supporting comprehensive system change that moves beyond “silos” for acute care, primary healthcare, public health, home care and mental healthcare); and
- community resources and policies (i.e., mobilizing community resources to meet the needs of patients even though these resources are not formally part of healthcare systems).(9;10)

Although primary prevention of chronic diseases is an important concern that, according to the Chronic Care Model, must be addressed at the population level, it was deemed out of the scope of this knowledge synthesis which focuses more specifically on optimal treatment approaches for people with multimorbidity.

The terms comorbidity and multimorbidity are often used interchangeably in the literature. However, there are notable distinctions between the two concepts.(1) Comorbidity has been defined as “any distinct additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study.”(11) As illustrated in the figure below (Figure 1), one disease is assuming a central place. According to Boyd et al., such conceptualization is inefficient and flawed in the presence of multiple chronic conditions unless one condition is “truly dominant in terms of the care and well-being of the individual.”(3)

In contrast, multimorbidity is defined as “the co-existence of two or more chronic conditions, where one is not necessarily more central than the others.”(3) As illustrated in the figure below (Figure 2), the concept of multimorbidity suggests that multiple diseases, syndromes and conditions may overlap and potentially interact, and consequently there may be interactions in their management.(3)

Figure 1: Conceptual representation of comorbidity (figure from Boyd et al., 2010)

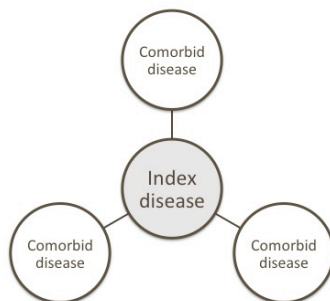
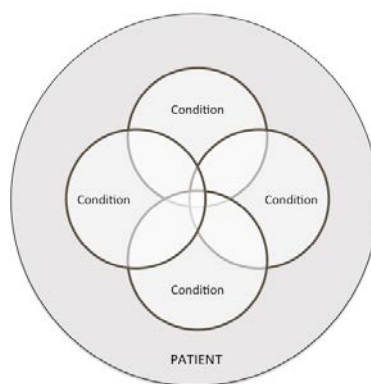


Figure 2: Conceptual representation of multimorbidity (figure from Boyd et al., 2010)



Multimorbidity is a recent field of research that remains conceptually immature. While the concept of multimorbidity is predominantly found in the literature, others have sometimes been used, such as polymorbidity, multipathology and polypathology.(12) In addition, there have been calls for greater conceptual clarity to distinguish multimorbidity from related concepts such as complexity, frailty and polypharmacy.(13)

Most definitions in the literature usually refer to multimorbidity as having two or more conditions. However, simply counting the number of conditions may be too restrictive.(14) Another element to consider in the conceptualization of multimorbidity is the severity of the conditions which can “range from mild and relatively asymptomatic to debilitating.”(15) Furthermore, the nature of these conditions are likely to influence the complexity of the treatment approaches.(15) Some patients may have concordant conditions representing the same overall pathophysiological risk profile which may be more likely to have a clear and integrated treatment plan (e.g., diabetes, hypertension, retinopathy and cardiovascular disease). In contrast, some patients may have discordant conditions which do not share the same pathophysiological risk profile. This may increase the risks of adverse clinical outcomes and growing demands for integrated healthcare delivery (e.g., asthma, diabetes and cancer).(16)

Efforts have been made to adapt existing comorbidity indexes to take into consideration the number of conditions and weight them according to their severity.(14;17) For instance, Hudon et al. adapted the Cumulative Illness Rating Scale (CIRS) to measure the burden of multimorbidity in primary care.(17) The modified version of the CIRS scale identifies 14 domains: 1) cardiac, 2) vascular, 3) hematological, 4) respiratory, 5) otorhinolaryngological and ophthalmological, 6) upper gastrointestinal, 7) lower gastrointestinal, 8) hepatic and pancreatic, (9) renal, 10) genitourinary, 11) musculoskeletal and tegumental,

12) neurological, 13) endocrine, metabolic and breast, and 14) psychiatric. The total theoretical score for the modified CIRS scale ranges from 0 to 56, based on scoring from 0 to 4 for each domain (0 = no problem; 1 = minor current problem or significant history; 2 = morbidity or moderate discomfort requiring primary care treatment; 3 = severe problem which creates constant significant discomfort and chronic problem difficult to control; and 4 = extremely severe problem requiring immediate treatment).(17)

The modified CIRS scale does not provide a cut-off score to determine multimorbidity.(14) However, some researchers in the multimorbidity community advocate for a definition of multimorbidity that focuses on three or more conditions (or three or more CIRS domains). While this definition may result in a lower prevalence of multimorbidity than the more predominant definition (i.e., two or more conditions), it may be better for identifying patients with higher needs which will be more clinically significant for people making treatment decisions.(18) Given this, we adopted this definition of multimorbidity (three or more conditions) for selecting research evidence included in the synthesis of findings about addressing multimorbidity (see Box 2 for an outline of our selection criteria), but we draw on the broader literature in outlining the problem of multimorbidity.

PROBLEM OF MULTIMORBIDITY

Efforts in addressing the challenges associated with providing care for people with multimorbidity will need to consider five key features of the problem: 1) the growing prevalence of multimorbidity; 2) the complexity of living with and treating multimorbidity; 3) the heavy burden on patients and caregivers; 4) the impact of multimorbidity on healthcare utilization and costs; and 5) the fragmentation of current programs and treatment strategies..

Growing prevalence of multimorbidity

Chronic diseases are a significant and growing challenge in Canada. The Health Council of Canada conducted an analysis based on the responses to the 2010 Commonwealth Fund International Health Policy Survey and found that among the sample of Canadians surveyed, 29% had one chronic condition, 15% had two chronic conditions, and 7% had three or more chronic conditions.(19) A second analysis based on the 2011 Commonwealth Fund International Health Policy Survey focused more specifically on sicker Canadians, (i.e., those who self-reported one or more chronic conditions and fair/poor health). The analysis revealed that 36% of sicker Canadians have three or more chronic conditions.(19)

While population-level data is not always readily available for people with three or more chronic conditions, current data suggests that the growing burden of multimorbidity disproportionately affects some groups in society. For example, 14% of Canadian women have two or more chronic conditions as compared to 11% of men, in 2005. The same data from 2005 also suggest that the risks of multimorbidity are growing steadily with age with only 13% of Canadian adults ages 20-39 reporting having one or more chronic conditions as compared to 71% of adults 60-79 years of age and 82% of adults 80 years and older.(20) In Ontario, 43% of adults over the age of 65 had two or more chronic conditions.(21) A review of community surveys also found that multimorbidity is affecting the most vulnerable groups in society (e.g., people who are less educated, have low incomes and/or are living in rural communities).(2;19;20) In 2005, 40% of low-income Canadians reported having one or more chronic conditions, compared to 27% of high-income Canadians. The poorest Canadians are almost three times as likely as the highest-income Canadians to have multimorbidity.(8)

Some of the major chronic conditions in Canada include arthritis, high blood pressure, mood disorders, diabetes, heart disease, cancer and chronic obstructive pulmonary disease.(20) These chronic conditions not only share common risk factors and conditions, but they also commonly occur together. For instance, 75% of Canadians with diabetes, heart disease, cancer or chronic obstructive pulmonary disease also have one or more other chronic conditions. Furthermore, more than 50% of people with high blood pressure or arthritis have at least one additional chronic condition, and 25% of people with mood disorders have other chronic conditions.(20)

Complexity of living with and treating multimorbidity

The health risks associated with having multimorbidity are numerous and varied. For instance, the literature suggests that people living with multimorbidity are more likely to die prematurely (22), experience adverse clinical events (1;23), have poorer quality of life, experience loss of physical functioning,(2;24;25) and have limited capacity to attain and sustain employment.(3)

Another challenge of living with and treating multimorbidity is the complex interplay between mental health and physical chronic conditions, with the latter having been described as the most common form of multimorbidity.(26) As observed by Mercer, the relationship between mental health and physical conditions appears to be “bidirectional.”(27) In other words, people with long-term physical conditions are more likely than the general population to experience mental health problems (e.g., anxiety, depression and other mood disorders), and people experiencing mental health problems are more likely to develop long-term physical conditions.(27) This relationship illustrates the need for more holistic approaches to treat multimorbidity that

bridge the physical, psychological and social dimensions of health.(28) However, addressing the mental health problems of people living with multimorbidity may be particularly challenging given the pervasive stigma associated with mental illness, which may discourage patients with multimorbidity to disclose their mental health concerns to their health professionals or caregivers.(27)

Treating patients with multimorbidity also raises a number of challenges and uncertainties. Decisions are often made “in the context of multiple, often ill defined, problems and fragmentary evidence.”(13) For instance, there may be uncertainty about the benefits and harms of simultaneous treatments. There is also the potential risk of worsening one condition by treating a coexisting one. It is also especially challenging to treat patients with multimorbidity because there are competing outcomes. As observed by Smith et al., “the more complex the case, the more we should think in terms of outcomes that are relevant across diseases, e.g., nutrition, living situations, function, symptom burden, survival, and active life expectancy.”(1) The challenge associated with balancing these competing outcomes highlights the need to engage patients and their informal caregivers to ensure that the prioritization process takes into account their values, needs and preferences.

Recent efforts to manage chronic conditions have led to the development of practice guidelines for the management of single chronic conditions or the management of multiple behavioural risk factors for patients with a chronic condition.(29) However, there is a paucity of guidelines for treating people with multimorbidity. The treatment burden arising from following several guidelines focusing on single conditions is also a recurring source of concern.(4;30) Despite the growing number of people with multiple chronic conditions, the majority of treatment guidelines focus on single diseases and rarely address how to optimally integrate care for people with multimorbidity.(16;31-33) As a result, following guideline recommendations of any single disease may become, in the context of multimorbidity, “impractical, irrelevant or even harmful.”(3)

Specifically, disease-focused guidelines may not be appropriate for treating patients with multimorbidity when diseases are discordant (i.e., are not related in their pathogenesis or treatment) (16;32;34;35) and problems may arise from:

- side effects of drugs that are prescribed as part of a treatment plan (e.g., drug-to-drug interactions from polypharmacy);
- exacerbation or variation in the clinical manifestations of one condition as a result of drugs that are prescribed for a different condition, or because of interactions between the conditions;
- single-disease guidelines leading to complex and sometimes contradictory treatments for multimorbidity; and
- patient factors precluding treating one or more conditions aggressively (e.g. cost of medicines, life expectancy, etc.).(31-33;35-37)

In addition, tying financial incentives to healthcare providers for guideline adherence for patients with multimorbidity may increase the burden placed on the patient for their care, increase the risks of drug-drug or drug-disease interactions, and lead to unrealistic expectations of physicians’ care.(31;35)

These challenges are also linked with limitations in how guidelines are developed. Guidelines are usually based on clinical trials which tend to exclude people with physical and mental comorbidities (and/or multimorbidity) as well as older adults, thereby limiting their applicability to these populations.(31;32;36) Other limitations that have been highlighted include the exclusion of information related to the burden of treatment for patients, short- and long-term goals, and other considerations related to patient preferences.(31;33;36) Tinetti et al outline the underlying tension between guideline development and clinical practice: “The developers of guidelines recognize that decisions about prescribing must be individualized, with patients’ overall health taken into account. Nevertheless, one of the hallmarks of quality-assurance programs is a reduction in the variation of practice patterns among providers.”(35)

Although the risks associated with multimorbidity are numerous, it is important to note that there are currently gaps in the literature. Indeed, a review conducted by the Chronic Illness Alliance in Australia to document problems related to safety and quality of services, as well as the risks and benefits of treatments for multiple and rare conditions and coordination of services, did not find articles written from the patients' perspectives or by patients on these matters.(30)

Heavy burden faced by patients with multimorbidity and their caregivers

Multimorbidity also places a heavy burden on patients and caregivers. Boyd et al. outline that people with multimorbidity have greater self-care needs, and that complex older patients are more likely to rely on informal/family caregivers.(3) The burden for patients and caregivers may take various forms such as managing multiple appointments with multiple healthcare professionals in multiple settings, following multiple and complex treatment regimens, as well as the stress the increased burden may generate.(38)

Patients with multimorbidity also report more negative experiences regarding their interactions with the health system. While sicker Canadians generally reported having timely access to care, they usually face three major problems: 1) significant cost barriers to accessing medication and follow-up care; 2) poor coordination and information flow among the various healthcare providers; and 3) lack of engagement in their care as compared to the general public. Consequently, sicker Canadians give the lowest ratings to the health system and to the care they have personally received.(19)

Impact of multimorbidity on healthcare utilization and costs

Multimorbidity also places a heavy burden on the health system in terms of healthcare utilization and costs. Adults with multimorbidity are significant users of healthcare services at all adult ages, and account for more than two-thirds of healthcare spending.(4) The Health Council of Canada estimates that patients with three or more chronic conditions represent 4% of the Canadian population, but use 9-10% of general practitioner and specialist consultations, 16% of nurse consultations and 23% of overnight stays in hospitals.(20) Furthermore, patients with multimorbidity are also at greater risk of potentially avoidable inpatient admissions or preventable complications in an inpatient setting, as well as being more susceptible to post-operative complications.(3;13) In Ontario, the estimated burden of chronic conditions amounts to just over 55% of the total direct and indirect healthcare costs, and this is estimated to rise.(39)

Fragmentation of current programs and treatment strategies for patients with multimorbidity

Current programs and treatment strategies are often described as “fragmented, incomplete, inefficient, and ineffective” for people living with multimorbidity,(3) which results in challenges for people getting the care they need.(13) Fragmentation often occurs because programs and treatment strategies are typically focused on single discordant chronic conditions (e.g., diabetes, cancer and mental illness) rather than offering comprehensive approaches to simultaneously manage multiple conditions. Thus, existing approaches based on the “single disease paradigm” appear increasingly inappropriate for the growing number of patients with multimorbidity.(40)

The context in which encounters between patients and their primary care physicians occur can also lead to suboptimal treatment approaches. Indeed, these encounters usually take the form of 15-minute, multi-agenda visits. Such context is likely to impede the provision of complete and adequate information to help patients manage their chronic conditions, and to engage them in collaborative decision-making.(41;42)

In addition, patients with multimorbidity often see multiple healthcare providers in different settings,(4;30) which may increase “the risks of errors and poor care coordination.”(43) Health system arrangements are often cited as exacerbating such fragmentation such as fee-for-service payment mechanisms relying on discrete International Classification of Diseases diagnostic codes that are not adapted to people with multiple chronic conditions.(4)

ADDRESSING MULTIMORBIDITY

In the following section, we present findings from the synthesis about the health risks, risk factors and protective factors faced by people with multimorbidity, programs and models for treating patients with multimorbidity, and promising guidelines for treating people with multimorbidity. Detailed information is provided in Box 2 about how the systematic reviews, primary studies and guidelines (or relevant literature) were identified in the knowledge synthesis, and the appendix outlines how the quality of the reviews was assessed.

Understanding health risks, risk factors and protective factors for people with multimorbidity

We identified three systematic reviews and five observational studies that outlined evidence regarding the health risks, risk factors and protective factors for people with multimorbidity. A summary of the key findings from these reviews and primary studies is provided in Table 1. For those who want to know more about the literature contained in Table 1 (or obtain citations), a fuller description of the systematic reviews and primary studies is provided in Appendix 1 and Appendix 2 respectively. A list of excluded primary studies that were not considered in this knowledge synthesis given our definition of multimorbidity (i.e., three or more conditions) is provided in Appendix 4.

A recent and medium-quality systematic review examined the prevalence of mental–physical multimorbidity in middle-aged and elderly long-term care residents without dementia, and found only one small study describing multimorbidity consisting of a wide range of chronic psychiatric and somatic conditions.(44) Findings from this study suggest that physical–mental multimorbidity is common among long-term care residents. The remaining studies included in the review show prevalence rates of comorbid physical and mental illnesses ranging from

Box 2: Identification and selection of research evidence

The knowledge synthesis includes the following types of literature:

- systematic reviews evaluating the health risks faced by and/or programs and models for treatment of people with multimorbidities;
- guidelines (or approaches to developing guidelines) outlining models for treating people with multiple morbidities;
- effectiveness studies evaluating programs and models for treatment of people with multimorbidity; and
- process evaluations (including qualitative research) of programs and models for treatment of people with multiple morbidities.

As outlined in the first section of this report, we defined multimorbidity as having three or more conditions for the purposes of selecting research evidence to include in the synthesis

We identified the above types of literature through several strategies: (1)

- a related articles search of PubMed in June 2012 using each of the 10 studies included in a recent systematic review and a hand search of the excluded references in the review. The PubMed search was limited to articles published in 2011 or later (the year the search was last conducted in the review). This PubMed search produced 649 documents after duplicate removal.
- a search of Medline in September 2012 using the ‘co-morbidity’ MeSH term (as the focus of the document) and limiting the search to the last 10 years (2002 to 24 September 2012). This search produced 851 documents.
- website searches of a number of Canadian and international organizations, including the Canadian Medical Association Infobase, Kaiser Permanente Guidelines International Network, the National Guideline Clearinghouse from the Agency for Healthcare Research and Quality, the United States Department of Health Human Services, the National Institute for Health and Clinical Excellence and the World Health Organization; and
- a search of recommended literature following a series of key informant interviews with experts in the field.

The results from the searches were assessed by two independent reviewers for inclusion. A document was included if it fit within the scope of one of the types documents outlined above and if it met our definition of multimorbidity for the synthesis (i.e., participants with three or more conditions).

0.5%–64.7%, which appear consistent with prevalence rates reported in other studies on community-dwelling older people. The review also found that long-term care residents with mental–physical multimorbidity were more likely to be younger, male and unmarried than other long-term care residents. They also had more cognitive impairment and problem behaviours, but no dementia. The review found no studies describing the care needs of long-term care residents with physical-mental health multimorbidity.

Another recent but low-quality review examined the occurrences, causes and consequences of multimorbidity in the elderly population.(45) The review found that very little is known about the risk factors for multimorbidity with no included studies having evaluated genetic background, biological causes (e.g., cholesterol, blood pressure and obesity), lifestyle factors (e.g., smoking, alcohol consumption, nutrition and physical activity), or environmental factors (e.g., air pollution and social environment) in relation to the development of multimorbidity. However, having a large social network was found to play a protective role. The review identified functional impairment, poor quality of life, high healthcare utilization and high out-of-pocket costs as major consequences of multimorbidity. In addition, the review also outlined that the number of diseases a patient had was consistently associated with increasing odds or risk for disability. However, there were inconsistent findings regarding the effect of multimorbidity on mortality for older adults with an increasing number of coexisting diseases significantly increasing the risk of mortality in some studies, but not in others.

Lastly, another recent and low-quality systematic review examined prospective cohort studies of multimorbidity in primary care to determine the nature, scope and key findings of the studies.(46) The review identified a series of risk factors for multimorbidity, including type of disease and psychosocial characteristics. Psychosocial risk factors (e.g., negative life events, an external health locus of control, and a social network of less than five people) were found to appear predominantly in conditions lacking a commonly known pathophysiological origin. The review also found that certain combinations of chronic conditions (e.g., chronic respiratory disease, congestive heart failure and diabetes) presented a greater risk for physical decline than others, and that other combinations (e.g., chronic respiratory disease and osteoarthritis) resulted in higher patient consultation rates. In addition, the review found that patients with multimorbidity use healthcare services more frequently as compared to those with only a single condition, and that multimorbidity predicted increased mortality rates. Furthermore, increasing multimorbidity predicted higher healthcare charges in an outpatient setting and an increased likelihood of inpatient admission or death. None of the included studies focused on the impact of health inequalities or socioeconomic status. Lastly, the review showed inconsistent findings of the impact of patients' income, sex, age and ethnicity on multimorbidity.

We also identified three cohort studies, one retrospective analysis and two cross-sectional surveys which assessed the health risks for people with multimorbidity. The cohort study revealed that multimorbidity is not only associated with elderly people, but it is also associated with a wide range of risk factors including family structure, marital status, education level, country of birth, medication use, health service use, existence of depressive symptoms, smoking status, overall health status and obesity (i.e., high waist-hip ratio and waist circumference).(47) The retrospective analysis revealed that the addition of each chronic condition led to an associated increase in primary care consultations, hospital out-patient visits, hospital admissions and total healthcare costs.(48) The two remaining cross-sectional surveys found that individuals in the poorest socioeconomic groups were more likely to develop multimorbidity at a younger age (49) and were more likely to die prematurely.(50) Indeed, one cross-sectional study revealed that the onset of multimorbidity occurred 10-15 years earlier in people living in the most socioeconomically deprived areas compared with the most affluent ones, and that the presence of a mental illness increased as the number of physical conditions increased.(50) Lastly, two prospective cohort studies exploring the quality of care received by older community-dwelling adults with multimorbidity concluded that multimorbidity is associated with better quality of care.(51;52) These somewhat counterintuitive findings have been the subject of much criticism as they contradict the literature on the subject and the experiences reported by patients with multimorbidity.(19;53) In addition, the findings have also been criticized based on conceptual and methodological limitations (e.g., looking at patients with multiple concordant conditions that have

considerable overlap in quality measures, and the scientific soundness of summing up quality indicators focusing on individual conditions rather than using quality indicators focusing on how care is integrated and coordinated).(54;55)

Table 1: Summary of key findings from the literature relevant to the health risks, risk factors and protective factors for multimorbidity

Categories of findings	Summary of key findings
Health and related risks of multimorbidity	<p><i>Findings from systematic reviews</i></p> <ul style="list-style-type: none"> • physical–mental multimorbidity is common among long-term care (LTC) residents and those with multimorbidity have been found to have more cognitive impairment and problem behaviours than those without;(44) • functional impairment, poor quality of life, high healthcare utilization and high out-of-pocket costs are common risks of multimorbidity;(45) • the higher number of diseases a patient had was found to consistently increase the odds or risk for disability.(45) • the effect of multimorbidity on mortality is unclear, with one review finding that it disproportionately increased mortality (46) and another finding inconsistent evidence;(45) • patients with multimorbidity have been found to use healthcare services more frequently as compared to those with only a single condition;(46) and • multimorbidity was found to be associated with increased healthcare charges in an outpatient setting and increase the likelihood of inpatient admission or death.(46) • certain combinations of chronic conditions have been found to increase the risk for physical decline and higher patient consultation rates;(46) <p><i>Findings from primary studies</i></p> <ul style="list-style-type: none"> • increase in the number of chronic conditions for a patient was found to be associated with an increase in primary care consultations, hospital out-patient visits, hospital admissions and total healthcare costs;(48) and • two studies exploring the quality of care received by older community-dwelling adults with multimorbidity concluded that multimorbidity is associated with better quality of care, although these somewhat counterintuitive findings have been the subject of much criticism (in terms of conceptual and methodological limitations that have been attributed to them).(51;52)
Risk factors for multimorbidity	<p><i>Findings from systematic reviews</i></p> <ul style="list-style-type: none"> • LTC residents with mental–physical multimorbidity were found to be more likely to be younger, male and unmarried than other LTC residents;(44) • psychosocial risk factors (e.g., negative life events, an external health locus of control, and a social network of less than five people) may appear predominantly in conditions lacking a commonly known pathophysiological origin; and(46) • there is inconsistent evidence of the impact of patients’ income, sex, age and ethnicity on multimorbidity.(46) <p><i>Findings from primary studies</i></p> <ul style="list-style-type: none"> • multimorbidity was found to be associated with a wide range of risk factors including family structure, marital status, education level, country of birth, medication use, health service use, existence of depressive symptoms, smoking status, overall health status and obesity;(47) and • individuals in the poorest socioeconomic groups were found to be more likely to develop multimorbidity at a younger age (49) and more likely to die prematurely.(50)
Protective factors for multimorbidity	<p><i>Findings from systematic reviews</i></p> <ul style="list-style-type: none"> • a large social network was found to play a protective role for the occurrence of multimorbidity.(45)

Characterizing programs and models for treating people with multimorbidity

In this section, we review the systematic reviews and primary studies about programs and models for treating people with multimorbidity identified through our searches. We first address the key findings from the literature examining the effectiveness of programs and models, and then we present the key findings from qualitative studies exploring the views and experiences of providers and patients regarding desired programs and models.

A summary of the key findings from the systematic reviews is provided in Table 2. For those who want to know more about the literature in this section (or obtain citations), a fuller description of the systematic reviews and primary studies is provided in Appendix 1 and Appendix 2 respectively. A list of excluded primary studies that were not considered in this knowledge synthesis given our definition of multimorbidity (i.e., three or more conditions) is provided in Appendix 4.

Effectiveness of programs and models

We found three systematic reviews and several primary studies that addressed the effectiveness of programs and models for treating people with multimorbidity. The first review, which is recent and of high quality, examined the effectiveness of interventions for improving outcomes in patients with multimorbidity in primary care and community settings.⁽¹⁾ All studies involved complex interventions with multiple elements, of which most involved a change to the organization of care delivery (i.e., case management and coordination of care, enhanced multidisciplinary team work, individual care plans, enhanced multidisciplinary community care, structured visits and structured telephone contact) or patient-oriented interventions (i.e., patient education, support for self-management and peer support) and, to a lesser extent, professional interventions (i.e., education and training of care coordinators). None of the included studies evaluated financial interventions (e.g., financial incentives to providers to reach treatment targets) or regulatory interventions (e.g., changes to local or national regulations designed to alter care delivery in order to improve outcomes). The majority of studies examined multimorbidity in older patients.

The same review also outlined that improving outcomes in patients with multimorbidity is difficult. However, findings suggested that interventions focusing on particular risk factors or on areas where patients with multimorbidity have difficulties (e.g., functional ability or medicine management) might be more effective, whereas organizational interventions that had a broader focus (e.g., case management or changes in care delivery) appeared less effective. However, the review found a tendency of organizational interventions (e.g., integrated treatment programs coordinated by care managers, or individualized pharmaceutical care plans implemented by multidisciplinary teams) to improve prescribing, medication use and adherence. Patient-oriented interventions that are not linked to healthcare delivery (e.g., diet and physical activity intervention with self-management support delivered by a health educator or self-management support programs led by lay individuals) also appeared less effective than those that are linked, with the exception of one study that examined interventions targeting functional difficulty and fall prevention which found significantly reduced mortality. The review also revealed that the effects of both organizational and patient-oriented interventions on health outcomes were mixed and inconclusive, particularly those relating to physical health outcomes. In addition, the effects of both types of interventions on psychosocial outcomes and outcomes relating to health service utilization were limited, but mixed effects on hospital admission rates were found.

Another recent review of medium quality examined the effectiveness of comprehensive care programs for patients with multimorbidity, and their impact on patients, informal caregivers and professional caregivers.⁽⁵⁶⁾ The programs included in this systematic review varied greatly in terms of target patient groups, settings, number of interventions and number of chronic care model components. The majority of programs included in the review incorporated interventions related to three or more components of the chronic care model. Almost all of them incorporated interventions related to delivery system design (e.g., case

managers, multidisciplinary teams, individualized care plans and home visits) and self-management support (e.g., involving patients in the design of their care plan, self-management education and self-management group sessions). Approximately half of the programs included interventions to support healthcare providers' decision-making (e.g., clinical guidelines, training teams to implement new protocols and supervising newly appointed case managers). Other interventions related to the chronic care model, such as clinical information systems (e.g. feedback sheets, electronic patient records and telehomecare units) and community resources (e.g. establishing access to community resources and partnerships with local community service centres) were less frequently observed in these comprehensive programs. A minority of programs incorporated interventions related to the organization of healthcare (e.g., committees to support new partnerships, employing management teams to support process and quality improvement and enabling infrastructure for innovations in chronic care). The review found inconsistent evidence of effectiveness of comprehensive care programs, but their effects appeared comparable to or more positive than those of usual care. However, there was moderate evidence of a beneficial effect of comprehensive care on inpatient healthcare utilization and healthcare costs, health behaviour of patients, perceived quality of care, and satisfaction of patients and caregivers. The review found insufficient evidence of a beneficial effect of comprehensive care on health-related quality of life in terms of mental functioning, medication use, outpatient healthcare utilization and healthcare costs. Lastly, the review found no evidence of a beneficial effect of comprehensive care on cognitive functioning, depressive symptoms, functional status, mortality, quality of life in terms of physical functioning, or caregiver burden. Given the substantial variation across programs the review was unable to determine which program components had positive effects and under which circumstances these programs may be most effective.

The third recent and high-quality systematic review examined the effectiveness of interventions to improve the appropriate use of polypharmacy and to reduce medication-related problems in older adults.⁽⁵⁷⁾ Among the 10 studies included in the review, one evaluated computerized decision support and nine evaluated complex and multifaceted pharmaceutical care (e.g., outreach interventions by pharmacists, screening of automated drug alerts by consultant pharmacists visiting nursing homes, and clinical pharmacist interventions in various settings) provided in a variety of settings. None of the included studies explored the effectiveness of professional, financial or regulatory interventions. The review found that both computerized decision support and pharmaceutical care interventions demonstrated a reduction in inappropriate medication use. For instance, the risks of serious adverse drug events were reduced significantly (35%) post-intervention in a study examining the effectiveness of geriatric evaluation and management clinics. However, the review found inconsistent evidence in four studies examining the effectiveness of pharmaceutical care (e.g., pharmacists offering a clinical pharmacy service in inpatient services on hospital wards, involving pharmacists in hospital discharge processes, offering medication reviews and counselling in community-based family medicine clinics, or offering a drug therapy management service) on hospital admissions. Given the current body of evidence, the authors of the review concluded that it remains unclear if interventions to improve polypharmacy result in clinically significant outcomes.

We also identified several primary studies reporting the findings of randomized controlled trials which found benefits for a diversity of interventions for treating people with multimorbidity. These include:

1. nurse-led interventions, such as multifaceted approaches that involve self-monitoring support, a medication review process, information and education support and motivational interviewing,⁽⁵⁸⁾ or nurse-led case management;⁽⁵⁹⁾
2. pharmacist-led shared medical appointments including multidisciplinary education and pharmacist-led behavioural and pharmacological interventions (for diabetes, lipids, smoking and blood pressure);⁽⁶⁰⁾
3. guided care teams including comprehensive assessments, evidence-based care planning, monthly monitoring of symptoms and adherence, transitional care, coordination of healthcare professionals, support for self-management, support for family caregivers, and enhanced access to community services;^(61;62) and

4. patient-centered, team-based collaborative care management (TEAMcare model) involving a primary care physician and a physician-supervised nurse in defining clinical goals and developing individualized care plans.(63-66)

Table 2: Summary of key findings from the synthesized literature relevant to the effectiveness of programs and models for treating people with multimorbidity

Summary of key findings	
<i>Findings from systematic reviews</i>	
Patient-oriented interventions	<ul style="list-style-type: none"> • the effect of patient-oriented interventions on health outcomes were mixed and inconclusive, but one review found limited and mixed effects on psychosocial outcomes and on outcomes relating to health service utilization;(1) • interventions focusing on particular risk factors or focusing on areas where patients with multimorbidity have difficulties appear to be more effective than organizational interventions with a broader focus;(1) • patient-oriented interventions that are not linked to the healthcare system (e.g., diet and physical activity intervention with self-management support delivered by a health educator) appeared less effective than those that are linked;(1)
Computerized decision support	<ul style="list-style-type: none"> • computerized decision support demonstrated a reduction in inappropriate medication use;(57) • the review found inconsistent evidence of the effects of such interventions on hospital admissions;(57) and • the authors concluded that it remains unclear if interventions to improve polypharmacy result in clinically significant outcomes.(57)
Organizational interventions	<ul style="list-style-type: none"> • the effect of organizational interventions on health outcomes were mixed and inconclusive, but one review found limited and mixed effects on psychosocial outcomes and on outcomes relating to health service utilization;(1) and • organizational interventions that have a specific focus (e.g., integrated treatment programs coordinated by care managers, or individualized pharmaceutical care plans implemented by multidisciplinary teams) tended to improve prescribing, medication use and adherence, whereas organizational interventions with a broad focus (e.g., case management or changes in care delivery) were less effective at achieving these outcomes;(1)
Comprehensive care programs	<ul style="list-style-type: none"> • while there is inconsistent evidence of effectiveness of comprehensive care programs, their effects appear comparable to or more positive than usual care;(56) • there was moderate evidence of a beneficial effect of comprehensive care on inpatient healthcare utilization and healthcare costs, health behaviour of patients, perceived quality of care, and satisfaction of patients and caregivers;(56) • there is insufficient evidence of a beneficial effect of comprehensive care on health-related quality of life (in terms of mental functioning), medication use, outpatient healthcare utilization and healthcare costs;(56) • there is no evidence of a beneficial effect of comprehensive care on cognitive functioning, depressive symptoms, functional status, mortality, quality of life (in terms of physical functioning), or caregiver burden;(56) and • given the substantial variation across programs, the authors could not draw definite conclusions to determine which program components had positive effects and under which circumstances these programs may be most effective.(56)
Pharmaceutical care	<ul style="list-style-type: none"> • pharmaceutical care (e.g., outreach interventions by pharmacists, screening of automated drug alerts by consultant pharmacists visiting nursing homes, and clinical pharmacist interventions in various settings) demonstrated a reduction in inappropriate medication use;(57) • the review found inconsistent evidence of these interventions on hospital admissions;(57) and • the authors concluded that it remains unclear if interventions to improve polypharmacy result in clinically significant outcomes.(57)
<i>Findings from primary studies</i>	
Nurse-led interventions	<ul style="list-style-type: none"> • multifaceted nurse-led interventions that involve self-monitoring support, a medication review process, information and education support and motivational interviewing showed some improvements in certain medical outcomes (e.g., reduction in systolic blood pressure);(58) and • nurse-led case management was shown to help patients with multimorbidity to have their hypertension, hyperglycemia and hyperlipidemia under control, and help them achieve certain treatment goals.(59)

Pharmacist-led shared medical appointments	<ul style="list-style-type: none"> • pharmacist-led shared medical appointments (including multidisciplinary education and pharmacist-led behavioural and pharmacological interventions) was shown to improve medical outcomes for depressed adults with multimorbidity (i.e., blood glucose monitoring, systolic blood pressure, low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol);(60) and • findings revealed there was no significant change in depressive symptoms among intervention patients.(60)
Guided care	<ul style="list-style-type: none"> • guided care (including comprehensive assessment, evidence-based care planning, monthly monitoring of symptoms and adherence, transitional care, coordination of healthcare professionals, support for self-management, support for family caregivers, and enhanced access to community service) was shown to reduce episodes of home healthcare, and reduced nursing facility admissions.(61;62)
TEAMcare model	<ul style="list-style-type: none"> • the TEAMCare model (i.e., a patient-centred, team-based collaborative care management model involving a primary care physician and a physician-supervised nurse in defining clinical goals and developing individualized care plans) was shown to improve quality of care, as well as medical and psychiatric outcomes.(63-66)

Views and experiences of patients and providers regarding programs and models

We identified seven qualitative studies, one cross-sectional study and a participatory action research study that outlined the views and experiences of patients and providers about programs and models designed to treat people with multimorbidity. Three of the qualitative studies explored the views and experiences of healthcare providers regarding the challenges that need to be overcome in order to offer optimal treatment approaches for people with multimorbidity. Key challenges identified from these studies include:

1. health professionals being overly cautious to work within their area of competency;(67;68)
2. tension between delivering care to meet quality targets and fulfilling the patient's expectations;(68;69)
3. limited consultation time to deal with people living with multimorbidity;(68;69) and
4. concerns about the patients' ability to adhere to complex regimens.(68)

Another three qualitative studies explored collaborative processes of care desired by patients with multimorbidity. The first study identified a need for convenient access to healthcare providers (via telephone, internet or in person); clear communication of individualized care plans; a single coordinator of care who could help prioritize their competing demands and ensure continuity of care; and empathetic providers ready to meet the unique and fluctuating needs of patients with multimorbidity.(70) The second study suggested that patients with multimorbidity were open to the use of technology for monitoring or educational purposes, but that such technology should never preclude human contact. Patients were also receptive to consulting non-physician providers to supplement the care provided by physicians.(71) The third study revealed that patients with multimorbidity were open to having nurses join family physicians in primary care practices, which could ensure greater accessibility.(72) However, patients emphasized the need to establish clear professional roles and scopes of practice with several expressing concerns regarding the shared roles between nurses and physicians, and having nurses perform medical acts that were traditionally within the scope of practice of physicians.(72)

One cross-sectional survey revealed that patients with multimorbidity have much more extensive self-management learning needs (i.e., how to monitor important symptoms, use medications correctly, manage medical emergencies, talk to and question physicians, and 18 other self-management skills) than patients with single chronic conditions.(73) The same cross-sectional survey also found that the preferences of patients with multimorbidity were consistent with team-based primary care, and that they are willing to see non-physician providers.(73)

Another qualitative study explored the use of electronic personal health applications to accommodate the management strategies and information preferences of older people living with multimorbidity and their caregivers. The study identified three key features of such applications: 1) providing links to authoritative and reliable information on side effects, drug interactions and other medication-related concerns in an accessible

way; 2) facilitating communication between patients, doctors and pharmacists through electronic messaging and health information exchange; and 3) providing patients with the ability to selectively disclose medication information to different providers.(74)

Lastly, a participatory action research project, which consisted of a one-day interactive collaborative workshop involving a broad array of Quebec-based stakeholders (e.g., health professionals, patients and family members, decision-makers and researchers) was conducted to recommend actions in primary care to improve cardiovascular disease prevention among patients with multimorbidity.(75) Using the chronic care model as a framework, the group recommended focusing on three domains that were perceived as essential: 1) electronic medical records; 2) collaborative practices; and 3) self-management support.

Identifying promising guidelines for treating people with multimorbidity and models for developing such guidelines

In this section, we review the guidelines for treatment of multimorbidity identified through our searches, and outline key findings and recommendations from the literature for developing guidelines focused specifically on treatment of multimorbidity. For those who want to know more about the literature in this section (or obtain citations), a fuller description of each document included in our analysis is provided in Appendix 3. A list of guidelines that were not considered in this knowledge synthesis given our definition of multimorbidity (i.e., three or more conditions) is provided in Appendix 5.

Existing guidelines for treatment of multimorbidity

We identified several overviews of the applicability of existing guidelines to multimorbidity, a small number of guidelines that provide implications or recommendations for treatment (but none that focused exclusively on multimorbidity) and examples of sets of principles that have been developed for the creation of multimorbidity guidelines. Of the six overviews of treatment guidelines that we identified, three assessed the applicability of identified guidelines for treating people with multimorbidity (32) and comorbidity,(16;76) and three focused on assessing the applicability of those identified for older adults with comorbid conditions. (31;33;77) From the three overviews with a broader scope, the one with a focus on multimorbidity found that it was inconsistently accounted for in the included guidelines, those that provided information had limited detail, cross-referencing to other guidelines of important comorbid conditions was rare, and none provided an assessment of the risks and benefits of the recommended treatments. Similarly, another overview of the quality and relevance of 16 Canadian clinical practice guidelines to the care of people with comorbidity found three guidelines that addressed specific recommendations for patients with two comorbid conditions, and one that provided recommendations for treating more than two concurrent comorbid conditions related to chronic kidney disease (outlined in more detail below).(76) In addition, while the third overview found that 17 of 20 guidelines provided considerations about comorbidity and considered it in treatment, none actually specified preferred actions for patients with more than one concurrent condition.(16) One of the overviews which focused on older adults evaluated guidelines addressing the top 10 common chronic diseases in Ontario, Canada. Of the 10 guidelines identified in this overview, eight mentioned people with comorbidities (but none about multiple comorbidities) and four provided information related to the burden of treatment on the patient (e.g., time needed to treat in order to provide a benefit in the context of life expectancy).(33) Similarly, the two remaining overviews about older adults found guidelines addressing comorbid conditions, but not for multiple comorbidities.(31;77)

As noted above, Fortin et al. (76) identified one guideline about chronic kidney disease in their overview as addressing multiple chronic conditions. However, while the guideline outlines how to manage several conditions and situations related to chronic kidney disease, it does not provide explicit guidance for managing multimorbidity (i.e., for people who have three or more of the conditions outlined within it). Despite this, the approach used in producing the guideline may provide helpful lessons for developing future guidelines for managing multimorbidity. Specifically, the guideline was developed by dividing chronic kidney disease into several topic areas (reduced kidney function, hypertension, diabetes, dyslipidemia, lifestyle management, proteinuria, anemia, mineral metabolism, initiation of renal replacement therapy, and comprehensive conservative management), assigning each area to providers (nephrologists) and topic experts who then conducted systematic reviews about each topic. Recommendations were then derived from the evidence, graded based on the strength of the evidence available, and then the guideline was reviewed by experts and external stakeholders to ensure consistency with other guidelines. To ensure consistency with guidelines for the two major risk factors for chronic kidney disease (cardiovascular disease and diabetic complications), the guideline was aligned with those from the Canadian Diabetes Association, the Canadian Hypertension Education Program and the Canadian Cardiovascular Society.

In our review of the National Institutes for Health and Clinical Excellence website, we identified another guideline about depression in adults who also have a chronic physical health problem.(78;79) The guideline provides a series of steps to consider, and within each step, advice is provided about the antidepressants that could be prescribed depending on possible physical comorbidities and co-prescribing scenarios. In addition, the guideline provides advice about collaborative care approaches for situations where there is evidence that they may improve patient outcomes. Lastly, while not focused on managing multimorbidity, we found several guidelines that either included recommendations related to multimorbidity or undertook a development process that may be informative for efforts to develop a multimorbidity guideline. For example, we found three guidelines about cardiovascular disease with one Canadian initiative that undertook a process to harmonize guidelines for the treatment and prevention of cardiovascular disease, (80) and two others providing recommendations on how to manage multiple chronic conditions.(81;82) The approach to harmonizing guidelines involved using a consensus model to consolidate 400 recommendations into 89 key recommendations for the management of cardiovascular risk factors.(80) From the other two cardiovascular guidelines, one included a brief discussion for managing several different conditions (hypertension, hyperlipidemia and diabetes mellitus), but not for managing multimorbidity (i.e., there was no discussion for how to simultaneously manage these conditions), (82) and the other included more specific recommendations regarding multimorbidity.(81) These included screening for risk factors, providing treatment recommendations for specific sets of conditions, referring patients with multimorbidity, highlighting the risks involved with polypharmacy, and considering end-of-life issues for elderly patients. Another guideline which focused on improving the care of older adults with diabetes mellitus took an approach to developing patient-centred care plans by identifying the major health threats to older diabetic patients and determining how physicians might approach prioritizing care for patients at different points along a spectrum of health status.(83;84)

In addition to these examples, we identified two documents developed through consensus panels and workgroups that provided guiding principles for managing multiple chronic conditions. The first consensus document focused on the care of older adults with multimorbidity and was developed through an expert panel convened by the American Geriatrics Society.(85;86) The document outlines guiding principles for physicians providing care for older adults with multimorbidity, and includes principles related to considering patient preferences, interpreting the available evidence, developing a prognosis, assessing clinical feasibility, optimizing care plans, and identifying barriers. Within these principles, several promising approaches were suggested which included using an interdisciplinary healthcare team, relying on caregivers in multiple settings, ensuring adequate training of physicians, having reimbursement structures that reward patient-centred medical care, and developing an evidence base relevant to older adults with multimorbidity. The second document we identified reported on a strategic framework for managing multiple chronic conditions that was created through a workgroup of representatives from each agency within the Department of Health and Human Services in the United States.(87) The strategic framework included an objective focused on addressing multiple chronic conditions in guidelines, and emphasized the need to ensure that those developing guidelines include information about the most common comorbidities that cluster with a particular condition and about how to manage risk factors to prevent the occurrence of additional chronic conditions. The strategy also noted the need to develop and maintain clearinghouses or repositories of chronic disease guidelines that label and incorporate information related to treating multiple chronic conditions.

Development of guidelines focused specifically on treatment of multimorbidity

While the availability of guidelines is limited, there are a number of recent initiatives that illustrate the growing momentum for the development of clinical practice guidelines for the care of people with multimorbidity. For instance, the PRISCUS research consortium (PRerequisite Sites for a new health Care model for elderly people with mUltiple morbidities) launched an ongoing project to develop consensus-based treatment standards, including initial management recommendations, for older patients with multimorbidity.(88) Other projects are currently led by researchers at the Johns Hopkins School of Medicine to review the development process of appropriate clinical practice guidelines for patients with multimorbidity.(89) Members of this

research team are involved in the American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity that we outline above. This group formulated the guiding principles for the care of older adults with multimorbidity, which guided the development of clinical tools (e.g., a multimorbidity pocket card identifying resources, tools and strategies for clinical practice) and public education resources (e.g., tip sheets for older adults with multimorbidity and their caregivers).(90) In addition, the National Institutes for Health and Clinical Excellence (NICE) recently announced the desire to develop methods that will allow them to provide advice in their guidelines on the management of patients with multimorbidity.(78;91) The announcement highlighted the depression guideline outlined above as one example of where they have already made progress towards this goal.

There has also been recent work published around the development and implementation of clinical practice guidelines (92-95) as well as initiatives to identify how to standardize clinical practice guidelines internationally through the work of the Guidelines International Network (GIN) (96) and through the World Health Organization's Guideline Review Committee.(97) While these initiatives focus on broader guideline development and implementation principles, they complement a growing literature of recommendations specifically about multimorbidity guidelines. As part of Appendix 3, we compiled a set of supplementary literature that provides recommendations for guideline development for multimorbidity. This supplementary literature is comprised of document/descriptive analyses, non-systematic reviews and discussion papers/comments/editorials, but they provide helpful insights into the types of recommendations being provided about treatment approaches and models for multimorbidity. The recommendations we identified from this literature include:

1. providing clear labelling and promotion of guidelines in clearinghouses that include information on people with multimorbidity;(87)
2. supporting collaborative guideline development to address the care of people with multimorbidity;(37)
3. including information on the most common multimorbidity disease clusters along with the main chronic condition, and on the management of risk factors to prevent the occurrence of additional chronic conditions;(31;37;87)
4. cross-referencing guidelines with each other when recommendations are synergistic or contradictory (32) or when patterns of multimorbidity are common;(98)
5. requiring chronic disease guidelines to include a section about multimorbidity that provides a summary of recommendations for diagnosis, severity assessments and treatments;(37)
6. developing and validating an instrument for assessing the applicability of guidelines to patients with multimorbidity (especially for older adults with multimorbidity);(33)
7. requiring guidelines to explicitly discuss the applicability of recommendations to patients with the most prevalent comorbid conditions, and discuss the quality of the evidence for these patients;(16;37)
8. developing a patient-centred approach (rather than one that is disease-oriented) to guideline development;(16;33-35;86;87;99)
9. considering health priorities, quality measurements, patient preferences, absolute risk reduction, life expectancy, and the marginal benefits and harms from polypharmacy or other treatments in patient-friendly language;(31-33;35-37;85;98)
10. including patient vignettes for common comorbid conditions;(32)
11. considering the feasibility of implementation of guidelines for patients with multimorbidity to minimize the burden placed on the patient;(37;86)
12. including older adults and patients with comorbid conditions in randomized trials and including the results of these trials in the development of guidelines;(16;31;34;35;86;87)
13. supporting better use of evidence available from trials, including economic modelling, time estimation models for benefits and harms, and structured expert elicitation methods for uncertainties in data including tools such as the Beers criteria for medication therapy in older adults;(37;85;98)
14. managing and understanding/interpreting heterogeneity of treatment effects in clinical trials;(37;86) and

15. utilizing technologies to enhance the use of guidelines in the care of people with multimorbidity, such as web-based applications for cross-referencing of guidelines (32) or electronic medical records (EMRs), to use risk calculators in the development of individualized guidelines.(99)

DISCUSSION

This knowledge synthesis was designed to support the actions of those involved with addressing the challenges associated with providing care for people with multimorbidity. The analysis of the literature revealed six key findings: 1) research on multimorbidity is still in its infancy; 2) people with multimorbidity are faced with a variety of serious health risks; 3) multimorbidity is not confined to older adults; 4) there is a need to better understand the risk and protective factors for multimorbidity; 5) promising programs and models are likely to be complex and multifaceted; and 6) there is growing consensus on a set of principles that can inform the development of programs, models and guidelines to treat people with multimorbidity. In the following section, a discussion is provided to further explore these key findings and their implications. We also identify a number of areas of progress that may contribute to our understanding of optimal treatment approaches for people with multimorbidity. Lastly, we discuss the strengths and limitations of the knowledge synthesis.

Research on multimorbidity is still in its infancy

The findings from this knowledge synthesis resonate with a recurring observation made in the literature that the “research on multimorbidity is still in its infancy.”(56). Multimorbidity is indeed a new area both conceptually and methodologically, which may explain the paucity of good quality research evidence.(1;18;56) Indeed, there is currently a lack of intervention studies that have been completed and published, especially for people with higher needs who may have three and more chronic conditions. As observed by Smith et al., “research to date has focused on description and impact rather than interventions.”(1) Furthermore, the substantial heterogeneity of programs for people with multimorbidity and the vast heterogeneity among patients with multimorbidity challenge our capacity to determine which components have the most beneficial effects and which patient groups may benefit most from these interventions.(56) Drawing conclusions from the literature about multimorbidity is further complicated given that trials assessing the effectiveness of comprehensive care programs or guidelines for chronic conditions often exclude patients with multimorbidity.(1;35) As a result, the current body of evidence limits our capacity to draw firm conclusions about the effectiveness of specific interventions.(1;56)

People with multimorbidity are faced with a variety of serious health risks

Our review of the evidence illustrates the extent to which people living with multimorbidity are facing a diversity of serious health risks such as, functional impairment, poor quality of life, mental illness, high healthcare utilization, high out-of-pocket costs, increased patient burden and mortality.

Multimorbidity is not confined to older adults

Another key finding of this synthesis is that multimorbidity is not confined to older adults. While most of the literature and interventions appear to focus predominantly on the impact of aging and multimorbidity, recent research evidence suggest that multimorbidity is increasingly common at a younger age, especially in the most socioeconomically deprived communities. Indeed, the onset of multimorbidity may occur more than a decade earlier in people living in the most socioeconomically deprived areas compared with the most affluent ones. Thus, interventions to address multimorbidity should not strictly focus on older adults.

This finding reveals the need to better understand the complex array of risk and protective factors (e.g., genetic, biological, socioeconomic and psychosocial) to inform the development of comprehensive programs and models for people with or at risk for, multimorbidity. This appears particularly important given that current research evidence suggests that interventions focusing on specific risk factors might be more effective.(1)

This finding also reveals the need to apply an equity lens to better understand how the problem may disproportionately affects certain groups. With respect to supporting optimal treatment approaches for people with multimorbidity in Ontario, groups that warrant particular attention in future research might include Aboriginal populations, ethnocultural communities, as well as rural and remote populations.

Promising programs and models are likely to be complex and multifaceted

Given the complex needs of people living with multimorbidity, it is generally expected that promising programs and models are likely to be complex and multifaceted (1;56), as reflected by the programs and models listed in our knowledge synthesis. Indeed, most interventions reviewed encompassed several key components of the Chronic Care Model, such as interventions to: ensure the delivery of effective and efficient clinical care (i.e., delivery system design); empower and prepare patients to manage their health and healthcare (i.e., self-management support); and promote clinical care that is consistent with the best available evidence and aligned with patients' values and preferences (i.e., decision support). Although decision support interventions are often observed in comprehensive programs and models for treating people with multimorbidity, the availability and value of current clinical guidelines remains limited. Indeed, we found that multimorbidity was inconsistently accounted for in the vast majority of clinical guidelines included in the synthesis. While some provided considerations about comorbidity and considered it in treatment plans, none actually specified preferred actions for patients with more than one concurrent condition or provided an assessment of the risks and benefits of the recommended treatments for people with multimorbidity.

Interventions related to the other components of the Chronic Care Model were less frequently observed in our review. For example, we found limited evidence about interventions to: organize patient and population-level data to facilitate efficient and effective care (i.e., clinical information systems); alter health system arrangements in order to promote a culture and mechanisms that promote safe and high-quality care for people with multimorbidity (i.e., health system); and mobilize the community to meet the needs of patients with multimorbidity (i.e., community resources and policies). Nevertheless, such interventions could play a key role in developing optimal treatment approaches for people with multimorbidity. Indeed, broader interventions to alter governance, financial and delivery arrangements within the health system may play an important role, given that the health system is not integrated in such a way to manage care across multiple specialties and settings. In addition, addressing multimorbidity may necessitate a reconfiguration of scopes of practice as well as funding and remuneration mechanisms that are adapted to address the complex needs of people with multimorbidity.(100)

Population-level interventions mobilizing community resources and policies also appear critical in light of current research evidence demonstrating the heavy burden on patients and caregivers, as well as the growing prevalence of multimorbidity in the most socioeconomically deprived communities. Thus, programs and models for approaches for treating people with multimorbidity will likely need to bridge medical care, social services and healthy public policies.(45;56)

Guiding principles for treating people with multimorbidity

According to Fortin et al., “models of collaborative, patient centered, and goal oriented care are more likely to meet the complex needs of patients with multimorbidity.”(13) This observation appears consistent with some of the key findings of our knowledge synthesis. For instance, recent qualitative studies exploring the views of patients with multimorbidity revealed their desire for collaborative processes of care which emphasize the patient's central role in managing their health and healthcare, (70;75) and that allow enough flexibility to meet their fluctuating needs.(70) These principles also resonate with those established by the expert panel convened by the American Geriatrics Society, which highlighted that physicians who are providing care for people with multimorbidity should elicit and incorporate patient preferences; interpret and apply the evidence specifically for older adults with multimorbidity; frame clinical management decisions within the context of risks, burdens and prognosis for older adults with multimorbidity; and consider treatment complexity and feasibility when making treatment decisions for people living with multimorbidity.(90;101) However, other

principles could guide application and adaptation of clinical guidelines as well as the actual development of guidelines that are aligned with the values, needs and preferences of people living with multimorbidity and their informal caregivers. To this end, the public and patient involvement toolkit developed by the G-I-N Public working group constitutes an important resource to support guideline producers in their public and patient involvement activities.(102) Given the paucity of robust research evidence, such principles and tools can guide the development of promising programs, models and guidelines for treating people with multimorbidity.

Areas of progress

As we have seen in the knowledge synthesis, a number of recent initiatives illustrate areas of progress for the development of comprehensive programs and models, as well as guidelines focused specifically on treatment of multimorbidity. However, a certain number of ongoing initiatives are worth mentioning.

A number of models and frameworks that may contribute to the development of optimal treatment approaches for people with multimorbidity have been described in the literature. Two recent examples from Canadian scholars include the implementation of an inter-organizational partnership to integrate care for children with medical complexity,(103) and a conceptual model for primary care practice focused on caring for patients with multimorbidity using communities of practice.(104) A third example is the recent launch of 19 Health Links in Ontario, which constitutes a promising initiative to support optimal treatment approaches for people with multimorbidity.(105) The mandate of these Health Links will be to support greater coordination of care and the development of personalized care plans. Each Health Link may include family doctors, specialists, hospitals, home care, long-term care and community support agencies. A fourth example is the performance measurement framework for people with multimorbidity released by the National Quality Forum in the United States.(106) This framework was developed to measure the quality of care for people with multimorbidity, but also constitutes a roadmap for the development of new healthcare programs and models for people with multimorbidity.

These examples illustrate that, while research on multimorbidity is still in its infancy, it remains a vibrant research domain. One group playing a key role in building momentum is the International Research Community on Multimorbidity (IRCM). (107) The IRCM constitutes a virtual community of practice supporting knowledge translation and exchange about multimorbidity. By linking researchers, healthcare professionals and other stakeholders, initiatives such as this can make important contributions to strengthening the conceptual and methodological underpinnings of this research domain, and act as a leading hub for improving treatment approaches for people with multimorbidity.

Strengths and limitations

The main strength of this knowledge synthesis is that it brings together the available research evidence from existing systematic reviews, primary research and treatment guidelines about health risks of multimorbidity, programs and models for treating multimorbidity, and promising treatment guidelines. As a result, we believe that this synthesis both adds to and complements existing syntheses that are available to help support those involved with addressing the challenges associated with providing care for people with multimorbidity. The main limitation relates to the difficulty of identifying research evidence related to multimorbidity. Conducting searches on a topic that is by definition about people living with combinations of different medical conditions is made difficult when research evidence is typically indexed by specific conditions and not combinations of them. To address this we used several strategies to identify literature for this synthesis, but there is still the possibility that important studies or reports were not identified.

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APPENDICES

The following tables provide detailed information about the systematic reviews, primary studies and guidelines (or relevant literature about guideline development) identified in the knowledge synthesis. The ensuing information was extracted from the following sources:

- Systematic reviews - the focus of the review, key findings, last year the literature was searched, the proportion of studies conducted in Canada and the proportion of studies focused on treating people with multimorbidity;
- Primary studies - the focus of the study, methods used, study sample, jurisdiction studied, key features of the intervention or processes of care and the study findings (based on the outcomes reported in the study); and
- Guidelines - the focus and scope of the guidelines, the methods used for their development (e.g., systematic review, consensus panel, etc.) and the key recommendations related to treatment for multimorbidity.

For the appendix table providing details about the systematic reviews, the fourth column presents a rating of the overall quality of each review. The quality of each review has been assessed using AMSTAR (A Measurement Tool to Assess Reviews), which rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. It is important to note that the AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to systematic reviews pertaining to delivery, financial, or governance arrangements within health systems. Where the denominator is not 11, an aspect of the tool was considered not relevant by the raters. In comparing ratings, it is therefore important to keep both parts of the score (i.e., the numerator and denominator) in mind. For example, a review that scores 8/8 is generally of comparable quality to a review scoring 11/11; both ratings are considered “high scores.” A high score signals that readers of the review can have a high level of confidence in its findings. A low score, on the other hand, does not mean that the review should be discarded, merely that less confidence can be placed in its findings and that the review needs to be examined closely to identify its limitations. (Lewin S, Oxman AD, Lavis JN, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP): 8. Deciding how much confidence to place in a systematic review. *Health Research Policy and Systems* 2009; 7 (Suppl1):S8).

All of the information provided in the appendix tables was taken into account by the authors in describing the findings in the knowledge synthesis.

Appendix 1: Systematic reviews that address programs and models for treating people with multimorbidity

Focus of systematic review	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that focused on multimorbidity
Systematic reviews about health risks for people with multimorbidity					
Examining the prevalence of mental–physical multimorbidity in middle-aged and elderly long-term care residents without dementia, the characteristics and care needs of these residents, and the determinants of mental disorders in physical disorders or vice versa (44)	The review found only one small study describing multimorbidity of a wide range of chronic psychiatric and somatic conditions in long-term care residents. Findings from this study suggest that physical–mental multimorbidity is common among long-term care residents. The remaining studies included in the review show prevalence rates of comorbid physical and mental illnesses (ranging from 0.5%–64.7%) which appear consistent with prevalence rates reported in other studies on community-dwelling older people. Long-term care residents with mental–physical multimorbidity were younger than other longer-term care residents and had more cognitive impairment and problem behaviours, but no dementia. No included study described the care needs of these residents.	2011	6/11 (AMSTAR rating from Program in Policy Decision-making)	0/17	17/17
Examining the occurrences, causes and consequences of multimorbidity in the elderly, and examining models and quality of care of persons with multimorbidity (45)	<p>The review found that multimorbidity affects more than half of the elderly population and that the prevalence increases in very old persons, women and people from lower social classes.</p> <p>Very little is known about the risk factors for multimorbidity. No study evaluating genetic background, biological causes (e.g., cholesterol, blood pressure, obesity), lifestyles (e.g., smoking, drinking, nutrition, physical activity), or environmental factors (air pollution, social environment) in relation to the development of multimorbidity were found.</p> <p>The review identified functional impairment, poor quality of life and high healthcare utilization and costs as major consequences of multimorbidity. A large social network seemed to play a protective role for the occurrence of multimorbidity.</p> <p>The review concluded that there is insufficient evidence to provide evidence-based care of patients affected by multimorbidity.</p>	2010	2/9 (AMSTAR rating from Program in Policy Decision-making)	4/41	41/41
Exploring prospective cohort studies of multimorbidity in primary care to determine their nature, scope and key findings, as well as the methodologies used (46)	<p>The review identified a series of risk factors for multimorbidity, including the type of disease and psychosocial characteristics of the patients (e.g., negative life events, an external health locus of control, and a social network of less than five people), which may be most important in conditions that lack a common pathophysiological origin.</p> <p>Certain combinations of chronic conditions (e.g., chronic respiratory disease, congestive heart failure and diabetes) were found to present a greater risk for physical decline than others. Some combinations (e.g., chronic respiratory disease and osteoarthritis) resulted in higher patient consultation rates.</p> <p>The review found that patients with multimorbidity have higher healthcare utilization than</p>	2010	2/9 (AMSTAR rating from Program in Policy Decision-making)	0/5	5/5

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	<p>those with only a single condition. Increasing multimorbidity predicted higher healthcare charges in an outpatient setting and an increased likelihood of inpatient admission or death.</p> <p>No study focused on the impact of health inequalities or socioeconomic status. The review found inconsistent findings of the impact of patients' income, sex, age and ethnicity on multimorbidity.</p>				
Systematic reviews about programs and models for treating people with multimorbidity					
<p>Examining the effectiveness of interventions for improving outcomes in patients with multimorbidity in primary care and community settings (40)</p>	<p>All studies in this review involved complex and multifaceted interventions, most predominantly a change to the organization of care delivery (i.e., case management or enhanced multidisciplinary team work) or patient-oriented interventions (i.e., patient education or support for self-management).</p> <p>The review found that these interventions have mixed effects, with a tendency to improve prescribing and medication adherence.</p> <p>More specifically, organizational interventions that have a broader focus (e.g., case management or changes in care delivery) appear less effective. Similarly, patient-oriented interventions that are not linked to healthcare delivery appear less effective, with the exception of one study that examined interventions targeting functional difficulty and fall prevention which found significantly reduced mortality.</p> <p>The results showed that improving outcomes in patients with multimorbidity is difficult, but interventions focusing on particular risk factors or functional difficulties might be more effective.</p>	2011	9/10 (AMSTAR rating from Program in Policy Decision-making)	2/10	10/10
<p>Examining the effectiveness of comprehensive care programs for patients with multimorbidity and their impact on patients, informal caregivers and professional caregivers (56)</p>	<p>The review included programs that varied greatly in terms of target patient groups, implementation settings, number of interventions, and number of chronic care model components.</p> <p>The review found moderate evidence of a beneficial effect of comprehensive care on inpatient healthcare utilization and healthcare costs, health behaviour of patients, perceived quality of care, and satisfaction of patients and caregivers.</p> <p>The review found insufficient evidence of a beneficial effect of comprehensive care on health-related quality of life in terms of mental functioning, medication use, and outpatient healthcare utilization and healthcare costs.</p> <p>The review found no evidence of a beneficial effect of comprehensive care on cognitive functioning, depressive symptoms, functional status, mortality, quality of life in terms of physical functioning, or caregiver burden.</p>	2011	5/9 (AMSTAR rating from Program in Policy Decision-making)	4/42	42/42
<p>Effectiveness of interventions in improving the appropriate use of polypharmacy and reducing medication-related problems in older people (57)</p>	<p>Among the 10 studies included in the review, one was a computerized decision support and nine were complex and multifaceted pharmaceutical care provided in a variety of settings. No included study explored the effectiveness of professional, financial or regulatory interventions.</p>	2009	11/11 (AMSTAR rating from Program in Policy Decision-making)	2/10	10/10

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	<p>The review found that these interventions demonstrated a reduction in inappropriate medication use. The number of adverse drug events also reduced significantly (35%) post-intervention in three studies. Thus, such interventions can be beneficial in reducing inappropriate prescribing and medication-related problems.</p> <p>However, the review found inconsistent evidence of the effectiveness of these interventions on hospital admissions and whether these resulted in clinically significant improvements.</p>				
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Appendix 2: Primary studies that address programs and models for treating people with multimorbidity

Focus of study	Methods	Sample description	Jurisdiction(s)	Key features of the intervention(s) or processes of care	Key findings
Primary studies about the health risks for people with multimorbidity					
Assess the prevalence of multimorbidity across a range of demographic, social, risk and protective factors (47)	Cohort study	Participants of the North West Adelaide Health Study	Australia	No intervention	The study revealed a range of factors associated with multimorbidity such as family structure, marital status, education level, country of birth, medication use, health service use, existence of depressive symptoms, smoking status, overall health status, high waist-hip ratio and waist circumference which vary according to age group.
Examining the distribution of multimorbidity and of comorbidity of physical and mental health disorders, in relation to age and socioeconomic deprivation (50)	Cross-sectional survey	A database of 1,751,841 people registered with 314 medical practices	Scotland	No intervention	The study found that 42.2% of all patients had one or more morbidities and 23.2% were living with multimorbidity. The findings revealed that the prevalence of multimorbidity increases substantially with age, and is present in most people aged 65 years and older. In addition, the study revealed that the onset of multimorbidity occurred 10-15 years earlier in people living in the most deprived areas compared with the most affluent, with socioeconomic deprivation particularly associated with multimorbidity that included mental health disorders (prevalence of both physical and mental health disorder 11.0%, 95% CI, 10.9-11.2% in most deprived area vs 5.9%, 95% CI, 5.8%-6.0% in least deprived). The presence of a mental health disorder increased as the number of physical morbidities increased (adjusted odds ratio 6.74, 95% CI 6.59-6.90 for five or more disorders vs 1.95, 1.93-1.98 for one disorder), and was much greater in more deprived than in less deprived people (2.28, 2.21-2.32 vs 1.08, 1.05-1.11).
Assess the feasibility of identifying younger individuals with multimorbidity at GP level and explore the effect of multimorbidity on the type and	Cross-sectional survey of GP records in two large urban general practices	Poorer individuals with at least three chronic conditions and aged between 45 and 64 years (n= 92 patients with multimorbidity, the median	Dublin, Ireland	No intervention	The study found that patients received a mean number of 7.5 medications and attended a mean number of 11.3 GP visits in the 12 months preceding the cross-sectional survey. The study identified a number of barriers to research into multimorbidity at the practice level such as difficulties relating to GP clinical softwares and variation in disease coding.

Focus of study	Methods	Sample description	Jurisdiction(s)	Key features of the intervention(s) or processes of care	Key findings
volume of health care delivered (49)		number of conditions was 4 per patient)			
Examine the prevalence and associated healthcare utilization and cost of patients with multimorbidity (48)	Retrospective analysis of patient records	Patients >50 years of age were eligible for the study which took place in three primary care practices in the West of Ireland (n=3309)	West of Ireland, Ireland	No intervention	The study found that the prevalence of multimorbidity (2 or more conditions) was 66.2% in those >50 years of age. Findings revealed that healthcare utilization and cost was significantly increased among patients with multimorbidity. After adjusting for age, gender and free medical care eligibility, the study found that the addition of each chronic condition led to an associated increase in primary care consultations (P = 0.001) (11.9 versus 3.7 for >4 conditions versus 0 conditions), hospital out-patient visits (P = 0.001) (3.6 versus 0.6 for >4 conditions versus 0 conditions); hospital admissions (P = 0.01) [adjusted odds ratio (OR) of 4.51 for >4 conditions versus 0 conditions] and total healthcare costs (P < 0.001) (€4,096.86 versus €760.20 for >4 conditions versus 0 conditions) over the previous 12 months.
Explore whether coexisting combinations of 8 common chronic conditions (i.e., hypertension, coronary artery disease, chronic obstructive pulmonary disease, osteoarthritis, diabetes mellitus, depression, osteoporosis, and atrial fibrillation or congestive heart failure) are associated with overall quality of care among vulnerable older	Prospective cohort study	A sample of community-dwelling persons 65 years of age or older who were at increased risk for death or functional decline within 2 years (n=372) enrolled in managed care organizations	USA	No intervention	The study found that multimorbidity was associated with greater overall quality scores. The mean proportion of quality indicators satisfied increased from 47% for elders with none of the pre-specified chronic conditions to 59% for those with 5 or 6 conditions (P < 0.0001), after controlling for number of office visits. The authors concluded that patients with greater multimorbidity received care that was better than would be expected based on the specific set of quality indicators they triggered.

Focus of study	Methods	Sample description	Jurisdiction(s)	Key features of the intervention(s) or processes of care	Key findings
patients (52)					
Explore the relationship between the quality of care and the number of medical conditions of patients (51)	Prospective cohort study	A sample of community-dwelling adult patients in the Community Quality Index study, the Assessing Care of Vulnerable Elders study, and the Veterans Health Administration project (n=7680)	USA	No intervention	The study found that the quality of care increased as the number of medical conditions increased. As evidence, each additional condition was associated with an increase in the quality score of 2.2% (95% confidence interval [CI], 1.7 to 2.7) in the Community Quality Index cohort, of 1.7% (95% CI, 1.1 to 2.4) in the Assessing Care of Vulnerable Elders cohort, and of 1.7% (95% CI, 0.7 to 2.8) in the Veterans Health Administration cohort. The relationship between the quality of care and the number of chronic conditions was little affected by adjustment for the difficulty of delivering the care recommended in a quality indicator and for the fact that, because of multiple conditions requiring the same care, a patient could be eligible to receive the same care process more than once. Adjustment for characteristics of patients, use of healthcare, and care provided by specialists diminished the relationship, but it remained positive.
Primary studies about programs and models for treating people with multimorbidity					
Evaluate the cost-effectiveness of a multicondition collaborative treatment program (TEAMcare) compared with usual primary care in outpatients with depression and poorly controlled diabetes or coronary heart disease (63)	Randomized controlled trial	Patients with depression and poorly controlled diabetes and/or risk factors for coronary heart disease (n=214)	Fourteen primary care clinics of an integrated healthcare system, Washington State, USA	The Multicondition Collaborative Care Management (TEAMcare) was a patient-centred, team-based collaborative care management intervention involving a primary care physician and physician-supervised nurse, which used a combination of principles from collaborative care depression interventions, the chronic care model, and integrated a treat-to-target medication strategy that was initially developed for diabetes. Clinical goals were identified and individualized care plans were developed.	The study found that, over a 24-month period, intervention patients had a mean of 114 (95% CI, 79 to 149) additional depression-free days and an estimated 0.335 (95% CI, -0.18 to 0.85) additional QALYs in comparison to patients receiving usual care. Intervention patients also had lower mean outpatient health costs of \$594 per patient (95% CI, -\$3241 to \$2053) relative to usual care patients.

Focus of study	Methods	Sample description	Jurisdiction(s)	Key features of the intervention(s) or processes of care	Key findings
Evaluate patient and physician behaviours (i.e., medication adherence, self-monitoring, and treatment adjustment) in achieving better outcomes for diabetes, coronary heart disease and depression (64)	Randomized controlled trial	Patients with depression and poorly controlled diabetes and/or risk factors for coronary heart disease (n=214)	Fourteen primary care clinics of an integrated healthcare system, Washington State, USA	The Multicondition Collaborative Care Management (TEAMcare) was a patient-centred, team-based collaborative care management intervention involving a primary care physician and physician-supervised nurse, which used a combination of principles from collaborative care depression interventions, the chronic care model, and integrated a treat-to-target medication strategy that was initially developed for diabetes. Clinical goals were identified and individualized care plans were developed.	<p>The study found that, among intervention patients, pharmacotherapy adjustment rates were six times higher for antidepressant medications, three times higher for insulin, nearly double for antihypertensive and oral hypoglycemic medications, and 1.6 times higher for lipid-lowering medications in comparison with usual care patients.</p> <p>The authors concluded that the intervention allowed for frequent treatment adjustments by primary care physicians, and increased self-monitoring by patients, which could ultimately improve control of diabetes, depression and heart disease without change in rates of medication adherence.</p>
Evaluate the effectiveness of integrated care for depression and chronic physical diseases in minimizing disability and improving quality of life (65)	Randomized controlled trial	Patients with depression and poorly controlled diabetes and/or risk factors for coronary heart disease (n=214)	Fourteen primary care clinics in Seattle, Washington, USA	The Multicondition Collaborative Care Management (TEAMcare) was a patient-centred, team-based collaborative care management intervention involving a primary care physician and physician-supervised nurse, which used a combination of principles from collaborative care depression interventions, the chronic care model, and integrated a treat-to-target medication strategy that was initially developed for diabetes. Clinical goals were identified and individualized care plans were developed.	The study found that disability and quality of life ratings significantly improved from baseline among the intervention patients at six and 12 months in comparison to patients who received usual care. Findings also revealed a trend toward greater improvement in disabilities in activities of daily living among intervention patients.

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Focus of study	Methods	Sample description	Jurisdiction(s)	Key features of the intervention(s) or processes of care	Key findings
Effectiveness of the TEAMcare program in improving disease control outcomes for diabetes and/or heart disease and coexisting depression (66)	Randomized controlled trial	Patients with depression and poorly controlled diabetes and/or risk factors for coronary heart disease (n=214)	Fourteen primary care clinics in Seattle, Washington, USA	The Multicondition Collaborative Care Management (TEAMcare) was a patient-centred, team-based collaborative care management intervention involving a primary care physician and physician-supervised nurse, which used a combination of principles from collaborative care depression interventions, the chronic care model, and integrated a treat-to-target medication strategy that was initially developed for diabetes. Clinical goals were identified and individualized care plans were developed.	The study found that the TEAMcare health services model was shown to improve quality of care and medical and psychiatric outcomes.
Evaluate the effectiveness and feasibility of an intervention to help people with diabetes and kidney disease improve blood pressure control and adherence to prescribed medications (58)	Randomized controlled trial	Patients over 18 years of age with diabetes, chronic kidney disease and systolic hypertension (n=75)	Australia	Multifactorial intervention consisted of self-monitoring of blood pressure, an individualized medication review, a 20-minute DVD, and fortnightly motivational interviewing follow-up telephone contact for 12 weeks for blood pressure control support and effective medication self-management. An intervention nurse with renal specialist and doctoral qualifications and trained in motivational interviewing delivered all components of the intervention.	The study found that the intervention was acceptable and feasible for this cohort of patients living with multimorbidity. Findings revealed no statistically significant differences between groups, although the mean systolic blood pressure reduction in the intervention group (n=36) was -6.9mmHg 95% CI (-13.8, -0.02) at nine months post-intervention.

Focus of study	Methods	Sample description	Jurisdiction(s)	Key features of the intervention(s) or processes of care	Key findings
Evaluate the effectiveness of pharmacist-led group shared medical appointment visits, Veterans Affairs Multidisciplinary Education in Diabetes and Intervention for Cardiac Risk Reduction in Depression, in patients with Type 2 diabetes mellitus (60)	Randomized controlled trial	Patients with diabetes with A1C>6.5% (n=88)	USA	VA-MEDIC-D consisted of four once-weekly, two-hour sessions followed by five monthly 90-minute group sessions. Each SMA session consisted of multidisciplinary education and pharmacist-led behavioural and pharmacologic interventions for diabetes, lipids, smoking and blood pressure. No pharmacologic interventions for depression were provided.	<p>The study found that the change in the proportion of intervention patients who achieved an A1C<7% was greater than the usual care (29.6% versus 11.9%). Intervention patients also attained reductions in systolic blood pressure, low-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol, but usual care patients only achieved reductions in non-high-density lipoprotein cholesterol.</p> <p>Findings revealed that neither intervention nor usual care patients received significant change in depressive symptoms.</p>
Evaluate the effectiveness of nurse case management in improving rates of control for hypertension, hyperglycemia and hyperlipidemia (59)	Randomized controlled trial	Diabetic patients with blood pressure> 140/90 mmHg, hemoglobin A(1c)> 9.0%, or LDL>100 mg/dL. (n=278 received case management and n=278 received usual care)	USA	Intervention patients received case management versus usual care over a one-year period.	<p>The study found that a greater number of individuals assigned to case management were able to have hypertension, hyperglycemia and hyperlipidemia under control (21.9% compared with 10.1% in the usual care group [P < 0.01]). Findings also revealed that a greater number of individuals assigned to case management achieved the individual treatment goals of HbA(1c) <8.0% (73.7 vs. 65.8%, P = 0.04) and BP <130/80 mmHg (45.0 vs. 25.4%, P < 0.01), but not for LDL <100 mg/dL (57.6 vs. 55.4%, P = 0.61), compared with those in the usual care group.</p>

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Focus of study	Methods	Sample description	Jurisdiction(s)	Key features of the intervention(s) or processes of care	Key findings
Evaluate the effectiveness of guided care teams on multimorbid older patients' use of health services (61)	Cluster-randomized controlled trial	Patients at high risk for using healthcare heavily in the future (n=850)	Three healthcare systems in the Baltimore, Maryland-Washington, DC, area (USA)	Guided care (i.e., comprehensive assessment, evidence-based care planning, monthly monitoring of symptoms and adherence, transitional care, coordination of healthcare professionals, support for self-management, support for family caregivers, and enhanced access to community services)	The study found that the only statistically significant overall effect of guided care was a reduction in episodes of home healthcare (odds ratio, 0.70; 95% confidence interval, 0.53-0.93). In addition, findings revealed that guided care also reduced skilled nursing facility admissions (odds ratio, 0.53; 95% confidence interval, 0.31-0.89) and days (0.48; 0.28-0.84).
Evaluate the effectiveness of guided care to improve quality of life and efficiency of resource use for older adults with multimorbidity (62)	Not specified	one-year pilot test in a community-based primary care practice	Maryland, US	Guided care (i.e., comprehensive assessment, evidence-based care planning, monthly monitoring of symptoms and adherence, transitional care, coordination of healthcare professionals, support for self-management, support for family caregivers, and enhanced access to community services)	The study found after a one-year pilot test that guided care is feasible, and acceptable to physicians, patients and caregivers.
Explore processes of care desired by elderly patients who have multimorbidities that may present competing demands for patients and providers (70)	Qualitative semi-structured interviews	Community-dwelling HMO members aged 65-84 who had, at a minimum, the combined conditions of diabetes, depression and osteoarthritis (n=26)	USA	No specific intervention or process of care	The study found that participants' desired processes of care included the following: the need for convenient access to providers (via telephone, internet or in person); clear communication of individualized care plans; and support from a single coordinator of care who could help prioritize their competing demands and continuity of relationships. Participants hoped that providers would listen to and acknowledge their needs, appreciate that these needs were unique and fluctuating, and also to have a caring attitude.

Focus of study	Methods	Sample description	Jurisdiction(s)	Key features of the intervention(s) or processes of care	Key findings
Explore the perceptions of general practitioners and nurses on service organization and clinical decision-making in patients with multimorbidity (69)	Qualitative semi-structured interviews	General practitioners (n=15) and practice nurses (n=10) in primary care	Manchester, UK	No specific intervention or process of care	The study found that primary care professionals identified tensions between delivering care to meet quality targets and fulfilling the patient's agenda, which are exacerbated when patients have multimorbidity. Professionals were aware of the inconvenience suffered by patients through attendance at multiple clinic appointments when care was structured around individual conditions. They also reported difficulties managing patients with multimorbidity in limited consultation time, which led to adoption of an 'additive-sequential' decision-making model which dealt with problems in priority order until consultation resources were exhausted, when further management was deferred. Other challenges included the need for patients to coordinate their care, the difficulties of self-management support in multimorbidity, and problems of making sense of the relationships between physical and mental health. Doctor and nurse accounts included limited consideration of multimorbidity in terms of the interactions between conditions, or synergies between management of different conditions
Explore how primary care clinicians approach treatment decision-making for these patients is critical to the design of interventions to improve the decision-making process (68)	Focus groups	Primary care clinicians (physicians, nurse practitioners and physician assistants) (n=40)	Academic, community, and Veterans Affairs-affiliated primary care practices in Connecticut, USA	No specific intervention or process of care	The study found that participants were concerned about their patients' ability to adhere to complex regimens derived from guideline-directed care. There was variability in beliefs regarding, and approaches to balancing, the benefits and harms of guideline-directed care. There was also variability regarding how the participants involved patients in the process of decision-making, with clinicians describing conflicts between their own and their patients' goals. The participants listed a number of barriers to making good treatment decisions, including the lack of outcome data, the role of specialists, patient and family expectations, and insufficient time and reimbursement.
Explore the medication self-management issues faced by older adults and caregivers that can be addressed by an electronic PHA (74)	Qualitative semi-structured interviews and focus groups	Patients 65 years or older, taking at least three prescription medications as outpatients, with two or more outpatient visits in the last year, and one or more	Colorado, USA	Using personal health applications to support medication self-management	The study identified five core themes regarding medication self-management challenges: seeking reliable medication information, maintaining autonomy in medication treatment decisions, worrying about taking too many medications, reconciling information discrepancies between allopathic and alternative medical therapies, and tracking and coordinating health information between multiple providers. PHA should have the following features to accommodate the management strategies and information preferences of this population: (1) provide links to authoritative and reliable information on side effects, drug interactions and other

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Focus of study	Methods	Sample description	Jurisdiction(s)	Key features of the intervention(s) or processes of care	Key findings
		chronic medical conditions (n=32) and family caregivers (n=2)			medication-related concerns in a clear way; (2) facilitate communication between patients, doctors and pharmacists through electronic messaging and health information exchange; and (3) provide patients the ability to selectively disclose medication information to different clinicians
Examine the self-management learning needs and willingness to see non-physician providers of patients with multimorbidity compared to patients with single chronic illnesses (73)	Cross-sectional survey	A sample of patients (n=720) from a single VHA healthcare system who are clustered in two groups: patients living with multimorbidity and patients with one chronic illness	USA	No specific intervention or process of care	<p>A higher percentage of multimorbidity patients compared to single morbidity patients were "definitely" willing to learn all 22 self-management skills, and of these only two were not significant. Compared to patients with single morbidity, a significantly higher percentage of patients with multimorbidity also reported that they were "definitely" willing to see six of 11 non-physician healthcare providers.</p> <p>Self-management learning needs of multimorbidity patients are extensive, and their preferences are consistent with team-based primary care. Alternative methods of providing support and chronic illness care may be needed to meet the needs of these complex patients.</p>
Explore the collaborative care needs and preferences in primary care patients with multiple chronic illnesses (71)	Focus groups	<p>Patients with two or more chronic illnesses identified by primary care physicians (n=60)</p> <p>Patients ranged in age from 30s to 80s, reflecting the diversity of the overall veteran patient population</p>	Eight geographically dispersed primary care clinics within the Veterans Health Administration, USA	No specific intervention or process of care	<p>Identified problems included poor functioning, negative psychological reactions, negative effects on relationships and interference with work or leisure. Polypharmacy was a major concern. Problematic interactions with providers and the healthcare system were also mentioned, often in relation to specialty care, and included incidents in which providers had ignored concerns or provided conflicting advice. Most participants, however, expressed overall satisfaction with their care and appreciation of their primary care physicians. Knowledge and skills deficits interfered with self-management. Participants were willing to use technology for monitoring or educational purposes if it did not preclude human contact, and were receptive to non-physician providers as long as they were used to augment, not eliminate, a physician's care.</p>

Focus of study	Methods	Sample description	Jurisdiction(s)	Key features of the intervention(s) or processes of care	Key findings
Explore pharmacist prescribing from the perspective of pharmacist prescribers, medical colleagues and key stakeholders (67)	Qualitative semi-structured interviews	Pharmacists (n=11), medical colleagues(n=11) and other key stakeholders (n=13)	Northern Ireland, UK	No specific intervention or process of care	Three major themes emerged in relation to pharmacist prescribing: the effect on patient care, challenges facing pharmacist prescribers, and the importance of the interprofessional team (where two or more different professions with varied, yet complementary experience work together with a common purpose). Pharmacist prescribing may have the potential to reduce the medication burden for patients (as reported by pharmacists) as pharmacists tend to provide a more comprehensive medication review than doctors; the additional time for consultations made this possible. Further research is required on how interprofessional team working can be maximized in the context of pharmacist prescribing, particularly in relation to the management of multi-morbidity.
Explore the perceptions and expectations of patients with multimorbidity regarding nurses' presence in primary care practices (72)	Qualitative semi-structured interviews	Primary care patients (n=18)	Québec, Canada	Integrating nurses in primary care practices	The study revealed that patients with multimorbidity were open to the involvement of nurses in primary care practices, which could ensure greater accessibility for them and for new patients. However, patients expressed a number of concerns regarding the shared roles between nurses and physicians, many sharing a more traditional view of nurses assisting physicians. Although patients were confident about the competence of nurses and recognized the need for greater interprofessional collaboration, they were also concerned about nurses performing medical acts that were within the scope of practice of physicians. Thus, patients called for the need to establish clear parameters for the professional roles and scopes of practice.
Identify challenges and priorities for action in primary care to improve cardiovascular disease prevention among patients with multimorbidity (75)	One –day interactive collaborative workshop (focus groups and nominal groups)	Physicians (n=6), nurses (n=6), community pharmacists (n=6), other health professionals (n=6), patients (n=6) and family members (n=6), decision-makers (n=6) and researchers (n=6)	Québec, Canada	Using the Chronic Care Model as a framework, participants in focus groups and nominal groups identified the challenges and priorities for action.	Providing appropriate support to lifestyle change in patients and implementing collaborative practices are challenging. Priorities for action relate to three CCM domains: (i) improve the clinical information system by providing computerized tools for interprofessional and interinstitutional communication; (ii) improve the organization of healthcare and delivery system design by enhancing interprofessional collaboration, especially with nurses and pharmacists, and creating care teams that include a case manager; and (iii) improve self-management support by giving patients access to nutritionists, to personalized healthcare plans including lifestyle recommendations, and to other resources (community resources, websites).

Appendix 3: Guidelines for treatment of people with multimorbidity

Document focus	Jurisdiction(s)	Type of study/document and methods used	Target population(s)	Key recommendations/findings
Guidelines and profiles of existing guidelines				
Management of chronic kidney disease (108)	Canada	<p><i>Type of study/document:</i> Guideline</p> <p><i>Methods used:</i> The management of chronic kidney disease was divided into key topic areas with each assigned to nephrologists and topic experts in the area who then conducted a systematic review for their assigned topic. Recommendations were derived from the evidence and then each was graded using the scheme developed by the Canadian Hypertension Education Program and used by the Canadian Society of Nephrology Guidelines Committee. The guideline was reviewed by experts and external stakeholders, including other relevant associations, to ensure consistency with other guidelines.</p>	Chronic kidney disease patients	<p>With the recognition that the major risk for patients with chronic kidney disease is death from cardiovascular disease or diabetic complications, the guideline was aligned with those from the Canadian Diabetes Association, the Canadian Hypertension Education Program and the Canadian Cardiovascular Society.</p> <p>Clinical recommendations are provided for referral of adult patients with reduced kidney function, hypertension, diabetes, dyslipidemia, lifestyle management, proteinuria, anemia, mineral metabolism, initiation of renal replacement therapy and comprehensive conservative management</p> <p>The guideline states that the complexity of chronic kidney disease requires a better understanding of the absolute and relative value of identifying and treating the myriad clinical and laboratory abnormalities that occur in the context of reduced kidney function.</p>
Creating guiding principles for physicians in the care of older adults with multimorbidity (90)	USA	<p><i>Type of study/document:</i> Consensus document developed through an expert panel</p> <p><i>Methods used:</i> An expert panel was convened based on expertise in different areas relevant to older adults with multimorbidity and geographic and training diversity. Through meetings, the panel proposed the domains for the document. A structured PubMed literature search strategy and a citation search of relevant articles were used. An external review was conducted and the document was posted on the American Geriatrics Society website for public comment.</p>	Older adults with multimorbidities	<p>Domains used in the organization of the document and relevant to the care of older adults with multimorbidity include patient preferences, interpreting the evidence, prognosis, clinical feasibility, optimizing therapies/care plans and barriers.</p> <p>Each guiding principle is discussed with a justification for the principle, how to use it in clinical practice, controversies and challenges, and ideas for a future research agenda.</p> <p>Promising approaches to overcoming barriers to implementation of guiding principles in the care of older adults with multimorbidity include: using an interdisciplinary healthcare team, relying on caregivers in multiple settings, ensuring adequate training of physicians, having reimbursement structures that reward patient-centred medical care, and developing an evidence base relevant to older adults with multimorbidity.</p>

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Improving the care of the older person with diabetes mellitus (83)	USA	<p><i>Type of study/document:</i> Guideline</p> <p><i>Methods used:</i> Reviewed existing guidelines and literature on each topic, construction of evidence tables that summarized the data from RCTs on each topic, modification of existing guidelines and development of new guidelines, and review and revision by members of an expert panel</p>	Older adults with diabetes	<p>Provided guiding principles for several areas of care for older adults with diabetes mellitus, which included the following: Aspirin use, smoking, hypertension, glycemic control, lipids, eye care, foot care, nephropathy, diabetes mellitus education, depression, polypharmacy, cognitive impairment, urinary incontinence, injurious falls and pain.</p> <p>In addition, the guideline provides the following general principles for care:</p> <ul style="list-style-type: none"> - establishing specific goals of care or target outcomes for persons with diabetes mellitus; - identifying and documenting targets for all aspects of care, such as management of hypertension, hyperlipidemia, hyperglycemia, mood disorder and screening and treatment of geriatric syndromes; - identifying contributing causes when goals of care are not met (e.g., difficulty with adhering to medications); - reviewing the feasibility of medication dosing and costs; - ensuring that care is kept simple and inexpensive through such practices as single daily dosing of drugs (or, when this is not feasible, twice daily dosing) - identifying when there is evidence of difficulty with adherence to a regimen that cannot or should not be simplified, and then having a physician, pharmacist, diabetes mellitus educator, or other healthcare practitioner provide: counselling of the patients, family members and caregivers; aids such as pill-dosing dispensers; and simplified approaches to care; and - referring to a specialist experienced in the care of older adults (e.g., endocrinologists, diabetologists, geriatricians, hypertension specialists, mental health specialists, diabetes mellitus educators and/or nutritionists) when outcomes are not being achieved.
Harmonizing guidelines for the prevention and treatment of cardiovascular disease: the C-CHANGE Initiative (Canadian	Canada	<p><i>Type of study/document:</i> Guideline (using consensus model)</p> <p><i>Methods used:</i> Phase 1. A collaborative relationship was built among eight core organizations that had previously published guidelines. A consensus model was created to harmonize guideline recommendations. The AGREE (Appraisal of</p>	Adults	<p>Multiple practice guidelines for similar conditions create challenges because of redundancy, discordance, different priorities for treatment and different evidence bases.</p> <p>Using a consensus model, more than 400 recommendations from eight separate guidelines were harmonized into 89 key recommendations for the management of cardiovascular risk factors.</p> <p>General recommendations include:</p>

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Cardiovascular Harmonization of National Guidelines Endeavour) (80)		Guidelines for Research and Evaluation) Collaboration was followed by? the C-CHANGE Initiative. Phase 2. Will include the development of an integrated review cycle to integrate the methods used by the C-CHANGE initiative with those of the core guideline groups for developing new and updated recommendations to account for coordination and consistency in quality.		<ul style="list-style-type: none"> - the risk of future cardiovascular events should be determined using established scoring systems in all patients older than 40 years; - treatment targets must be based on the individual patient’s level of risk; - recommended health behaviours for all patients include no smoking, following a diet capable of promoting energy balance and a healthy body weight, and adequate weekly physical activity; and - a combination of modifications to health behaviours and pharmacologic interventions will be required in most patients at high and moderate risk of cardiovascular events to meet treatment targets. <p>Specific recommendations are provided for screening, diagnostic and risk stratification strategies; treatment targets; health behaviour interventions; and pharmacologic therapy.</p> <p>The C-CHANGE Initiative’s strategies for harmonization and integration of clinical practice guidelines include:</p> <ul style="list-style-type: none"> - developing a standardized database of evidence that is continually updated; - reviewing collaborative evidence among national and international organizations; - using a common metric to assess the quality of evidence and strength of recommendations; - developing clinical practice recommendations concerning issues that are important to patients and clinicians; - including relevant stakeholders, with consideration of representatives for patients, on guideline panels; - considering comorbidities and the importance of harmonization in the development of guidelines; - identifying the best tools for implementation for both clinicians and patients; - addressing potential and established conflicts of interest and ensuring transparency of sponsorship; - maintaining a collaboration of national and international organizations; - developing methods for effectively establishing clinical outcomes; and - examining collaborative models for funding the development and implementation of guidelines, such as funded dissemination strategies or licensing of tools adapted for electronic health records.

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Canadian Cardiovascular Society guidelines on the diagnosis and management of heart failure (81)	Canada	<i>Type of study/document:</i> Guideline <i>Methods used:</i> Evidence was critically reviewed by a multi-disciplinary panel and a second panel reviewed those recommendations.	Patients with heart failure	Recommendations regarding multiple morbidities: <ul style="list-style-type: none"> - screening for diseases that can cause heart failure should be determined by clinical suspicion in individual patients (specific conditions listed); - treatment recommendations are provided for specific sets of conditions, most are other cardiovascular conditions; - referral for patients with multiple comorbidities is recommended; - cautions are provided for polypharmacy; - general principles under polypharmacy section outline that patients with heart failure are generally elderly and have multiple comorbidities, and therefore the addition of multidrug therapy for heart failure adds to an already complex pharmacological regimen. As such, drug interactions, additive adverse effects (such as hypotension) and poor medication adherence occur commonly; and - recommendations provided for the assessment of the elderly heart failure patient including end-of-life issues
American College of Cardiology/ American Heart Association 2005 Clinical practice guideline for heart failure (82)	USA	<i>Type of study/document:</i> Guideline <i>Methods used:</i> A 15-member multi-group panel wrote the guideline using available evidence	Adults with chronic heart failure	This guideline has specific sections discussing heart failure in the elderly and in patients with comorbid conditions including coronary artery disease, supraventricular arrhythmias, renal insufficiency, pulmonary disease, cancer, thyroid disease, hepatitis C and HIV, and anemia. The only treatment of multiple comorbidities discussed is hypertension, hyperlipidemia and diabetes mellitus.
Developing a strategic framework for managing multiple chronic conditions (87)	USA	<i>Type of study/document:</i> Consensus document <i>Methods used:</i> The United States Department of Health and Human Services (DHHS) created a workgroup with representatives from each agency within HHS. The draft of the document was announced in the Federal Register and feedback from 250 stakeholder organizations and others were incorporated in the final version.	Adults with multiple chronic conditions	One objective of the document was focused on addressing multiple chronic conditions in guidelines. As part of this objective, proposed strategies include the need to ensure that: <ul style="list-style-type: none"> - developers of guidelines include information on the most common comorbidities clustering with the incident chronic condition, and on the management of risk factors to prevent the occurrence of additional chronic conditions; and - clearinghouses or repositories of chronic disease guidelines encourage labelling and promotion of selected guidelines that incorporate information on individuals with multiple chronic conditions
Evaluation of the applicability of clinical practice	USA	<i>Type of study/document:</i> Overview of treatment guidelines	Patients 65 years or older with comorbidities	Of the nine clinical practice guidelines studied, four addressed older individuals with multiple comorbidities; seven addressed older individuals and included recommendations for one comorbid condition; four provided specific

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guidelines for older individuals with several comorbid diseases and implications for pay for performance (31)		<p><i>Methods used:</i> The National Health Interview Survey and a nationally representative sample of Medicare beneficiaries were used to select the most prevalent chronic diseases managed in primary care in this population. The authors excluded depression and dementia to focus on adherence to recommendations and understanding of health information. The National Guideline Clearinghouse was used to locate evidence-based clinical practice guidelines (CPGs) for each chronic disease. The CPGs were then assessed using previously established standards for quality of CPGs: describing the target population, grading the quality of evidence supporting the recommendations, discussing therapeutic goals, addressing quality of life, incorporating patient preferences, and including competing risks and burden of treatment for patients and caregivers.</p> <p>The feasibility of combining the treatment recommendations from relevant CPGs for a hypothetical 79-yr-old woman with five chronic conditions was then examined.</p>	<p>including: hypertension, chronic heart failure, stable angina, atrial fibrillation, hypercholesterolemia, diabetes mellitus, osteoarthritis, chronic obstructive pulmonary disease and osteoporosis.</p>	<p>recommendations for patients with several comorbid conditions; one addressed time needed to treat in order to benefit from treatment in the context of life expectancy; none addressed burden of comprehensive treatment on patients or caregivers; three acknowledged patients' financial burden; none addressed balancing short- and long-term goals; and seven discussed patient preferences but did not provide guidance on incorporating these preferences.</p> <p>The hypothetical patient exercise found that the patient would take 12 different medications with 19 different dosings divided five times per day, costing close to \$4,000 per year with Medicare part D. There were many non-pharmacological therapies recommended and some were contradictory. Two to four primary care visits and one ophthalmologic visit per year would be possible for monitoring, but a 15-minute visit would not be sufficient to address all the elements of the treatment plan.</p>
Analysis of the quality and relevance of Canadian clinical practice guidelines to the care of adults with comorbidity (76)	Canada	<p><i>Type of study/document:</i> Overview of treatment guidelines</p> <p><i>Methods used:</i> 16 chronic medical conditions were selected according to their frequency of occurrence, complexity of treatment, and pertinence to primary care. Recent Canadian clinical guidelines (2004 - 2009) on these conditions, published in English or French, were then identified. The guidelines were assessed according to their relevance to the care of patients with comorbidity, and quality was</p>	<p>Patients with comorbid conditions involving 16 chronic medical conditions: dyslipidemia, chronic impaired renal function, anxiety, heart failure, coagulopathy,</p>	<p>Of the 16 guidelines identified, nine addressed treatment for patients with multiple chronic conditions, three of which focused on older patients. Fifteen guidelines included specific recommendations for patients with one concurrent condition; only three guidelines addressed specific recommendations for patients with two comorbid conditions, and one for more than two concurrent comorbid conditions (chronic kidney disease). Quality of the evaluated guidelines was good to very good in four out of the six domains measured using the AGREE instrument with lower scores observed for the domains about stakeholder involvement and applicability.</p>

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		assessed using the AGREE instrument.	obesity, atrial fibrillation, glaucoma, peripheral arterial disease, chronic obstructive pulmonary disease (COPD), asthma, osteoporosis, rheumatoid arthritis, Type 2 diabetes, dementia, high blood pressure, hypothyroidism, and depression	
Assessing the relevance of Australian clinical guidelines to the care of older people with multiple comorbid conditions (77)	Australia	<p><i>Type of study/document:</i> Overview of treatment guidelines</p> <p><i>Methods used:</i> National guidelines for the chronic conditions listed as National Health Priority Areas were included. The quality of guidelines was assessed using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument, and the relevance of the guidelines to the care of older people with multiple illnesses was assessed by means of a specific, 14-item, instrument developed in a previous study.</p>	Patients with comorbid conditions including: cardiovascular health, diabetes mellitus, mental health, asthma, arthritis and musculoskeletal conditions, and cancer	Out of 17 guidelines, half of the guidelines addressed treatment for older patients or for patients with one comorbid condition, but only one addressed treatment for older patients with multiple comorbid conditions
Assessing clinical guidelines in the U.K. for inclusion of people with multimorbidity (32)	UK	<p><i>Type of study/document:</i> Overview of treatment guidelines</p> <p><i>Methods used:</i> Guidelines published within the last five years for five common conditions in the United Kingdom were selected for the analysis. Information was extracted from the guidelines</p>	Patients with comorbidities including: diabetes Type 2, previous myocardial infarction, osteoarthritis,	<p>All guidelines considered older patients to varying degrees. None commented on the quality of the evidence in older people or on the generalizability of trial evidence.</p> <p>Comorbidity was inconsistently accounted for in the guidelines with little detailed discussion. Cross-referencing to other guidelines for important comorbidities was uncommon, and no information was provided on the relative risks and benefits of the different treatments recommended.</p>

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		<p>and available quick reference guides. The review examined whether and how guideline recommendations gave specific advice about: 1) care for older people or those with comorbidities; 2) providing patient-centred care by accounting for patient choice and preferences; and 3) promoting adherence to treatment recommendations. The guidelines were then categorized according to the extent to which they discussed these criteria using three categories: 1) none or minimal (criteria used on two or fewer occasions), 2) moderate (criteria used on three to five occasions) or 3) extensive (criteria used on five or more occasions).</p> <p>Two hypothetical patients were created to illustrate the potential cumulative impact of applying single-disease recommendations to people with multimorbidity.</p>	<p>chronic obstructive pulmonary disease, and depression.</p>	<p>All the guidelines generically emphasized the importance of tailoring treatment to patients' needs and preferences, but specific considerations were varied.</p> <p>Dealing with adherence to treatment recommendations was also varied.</p> <p>The burden placed on patients and caregivers as a result of applying the five guidelines to hypothetical patients was considerable. The guidelines did not explicitly address the treatment burden or adherence, nor provide any guidance on the relative risks and benefits of the many treatments recommended.</p> <p>Linking guideline recommendations with targets/ financial incentives causes concern of driving polypharmacy and treatments which may not benefit the patient.</p> <p>Recommendations provided for improving clinical guidelines include:</p> <ul style="list-style-type: none"> - providing summarized and comparable information about the relative benefits and risks of different recommended treatments to inform prioritization in patients with multimorbidity; - ensuring that existing guidelines explicitly cross-reference each other when recommendations are synergistic or contradictory, which would include identifying high-risk interactions between recommended treatments and other commonly prescribed drugs (e.g., through an internet-based format); - providing a small number of specific patient case examples in guidelines for common combinations or comorbidity seen in clinical practice; - noting within guidelines specific advice for practitioners when treating older patients (e.g. drug doses or class); and - increasing the participation of older people in clinical trials.
<p>Assessing the applicability of clinical practice guidelines for elderly patients with comorbidities (33)</p>	<p>Canada</p>	<p><i>Type of study/ document:</i> Overview of treatment guidelines</p> <p><i>Methods used:</i> The top 10 prescription claims were mapped to the 10 most common chronic diseases managed by primary care physicians in Ontario. Clinical practice guidelines (CPGs) developed by Canadian organizations or societies were selected</p>	<p>Patients 65 years or older with comorbidities including: osteoarthritis, osteoporosis, dyslipidemia, diabetes,</p>	<p>Of the 10 clinical practice guidelines identified, seven mentioned treatment of the elderly, eight mentioned people with comorbidities, four indicated the time needed to treat to benefit in the context of life expectancy, five discussed barriers to implementation of the clinical practice guideline and seven discussed the quality of evidence.</p> <p>Recommendations provided included the need for guideline developers to include more detailed information on management of elderly patients, which would involve</p>

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		based on relevance and likelihood of use by family physicians. Checklists based on published applicability measures for elderly patients with multiple morbidities were used to extract information from the CPGs.	hypertension, congestive heart failure, gastroesophageal reflux disease, chronic obstructive pulmonary disease, depression and dementia	placing emphasis on eliciting patient and caregiver concerns, setting clinical priorities, managing expectations (particularly around prognosis), and fostering optimum communication. Guidelines should consider an open discussion about patient's preferences, benefits of intervention in advanced age, time to benefit from treatment, trade-offs for function over disease control, and acknowledgment of uncertainty.
Assessment of the applicability of guidelines to patients with comorbid conditions (16)	International	<p><i>Type of study/document:</i> Overview of treatment guidelines</p> <p><i>Methods used:</i> Chronic conditions to inform guideline selection were chosen based on prevalence and impact on quality of life. Data were abstracted from each guideline on the extent that comorbidity was addressed (general comments, specific recommendations), the type of comorbidity discussed (concordant, discordant), and the supporting evidence of the comorbidity-related recommendations (level of evidence, translation of evidence).</p>	Patients with comorbid conditions: major depressive disorder, diabetes Type 2, chronic obstructive pulmonary disease, and osteoarthritis	<p>Of the 20 guidelines that were identified, 17 addressed comorbidity, eight provided comorbidity prevalence data, 16 addressed screening/diagnosing for comorbidity, 17 considered comorbidity in treatment, 12 included patient-centred aspects and 14 included specific comorbidity-related treatment recommendations.</p> <p>Most guidelines do not provide explicit guidance on treatment of patients with specific combinations of diseases, especially with discordant combinations. None of these guidelines specify a preferred action for patients with more than one concurrent condition. In addition, no systematic approach is used by guideline development groups for addressing comorbidity in guidelines.</p> <p>In general, the evidence base for patients with multiple chronic conditions is limited.</p> <p>Recommendations from the authors included the need for guidelines to be more explicit about the applicability of their recommendations to patients with the most prevalent comorbid conditions, and to provide a discussion of the quality and directness of the evidence for these patients.</p>
Supplementary literature outlining models and/or recommendations for guideline development for multimorbidity				
Assessing the representation of individuals 80 years of age and older in chronic disease clinical	Canada	<p><i>Type of study/document:</i> Descriptive analysis clinical practice guidelines</p> <p><i>Methods used:</i> Five chronic conditions were selected based on percent of population affected, effect on quality of life, Canadian healthcare</p>	Patients 80 years or older with a chronic condition: diabetes, heart failure, hypertension,	<p>Out of 2272 studies used as evidence for the recommendations in the clinical practice guidelines and that provided a mean age for their sample populations, only 1.4% had a mean age of 80 years or older. Most recommendations for older individuals in these guidelines are for "younger" older patients (65-79 yrs).</p> <p>Of the 14 clinical practice guidelines identified, all addressed treatment for patients 65</p>

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practice guidelines (36)		costs, and availability of regularly updated clinical practice guidelines. Descriptive analysis was performed on all references published in the guidelines to determine inclusion of older individuals. Clinical practice guidelines were reviewed for age-specific recommendations.	osteoporosis and stroke	<p>or older, six addressed treatment for frail or 80 years old and over patients, 13 addressed treatment for one additional chronic disease, and three addressed treatment for multiple comorbid conditions</p> <p>The study recommendations included the need for further investigation into the applicability of research findings for populations in advanced old age. It was also suggested that a new approach to account for possible interactions of multiple recommendations and multiple medications, and mental and functional issues, should be considered.</p>
Developing a general framework for a patient-centered plan of care for patients with diabetes and a complex health status (84)	USA	<p><i>Type of study/document:</i> Discussion paper</p> <p><i>Methods used:</i> Not applicable. Provides a discussion about how the “Guidelines for improving the care of the older person with diabetes mellitus” attempts to help clinicians develop a general framework for creating a patient-centred plan of care. Discussion includes three hypothetical patients with diabetes.</p>	Older adults with diabetes mellitus II and complex health status	<p>The “Guidelines for improving the care of the older person with diabetes mellitus” has advanced the way guidelines are developed by providing a rationale for prioritizing and individualizing evidence-based clinical management of older adults with complex health status. The creators of the guideline asked: 1) what are the major health threats to older diabetic patients; and 2) how might physicians prioritize healthcare recommendations for patients at the extremes of health status and those in between.</p> <p>Recommendations for creating a patient-centred care plan for an older adult using the “Guideline for improving the care of the older persons with diabetes mellitus:”</p> <ul style="list-style-type: none"> - estimate the patient’s approximate life expectancy compared with the median for individuals of that age-sex cohort by considering the presence or absence of unusually good or poor health and function; - establish the patient’s healthcare goals and preferences for treatment; - evaluate and manage geriatric syndromes consistent with the patient’s goals and the impact that these may have on the management of other medical conditions; - help the patient prioritize treatment options for diabetes and other conditions consistent with the patient’s goals and treatment preferences, and the magnitude and time to benefit in the context of the patient’s overall health; - remember that for older adults with diabetes and an absence of significant medical illness or disability, intensive management of blood pressure and lipid levels and use of Aspirin therapy have the greatest chance of benefit within two-three years; - consider intensive glycemic targets for older adults with a life expectancy of longer than eight years and a low risk of hypoglycemia, and for those who have existing microvascular complications who may benefit from intensive glycemic management in a shorter time frame; and - frail older adults, those with a high burden of illness, difficulty adhering to therapy,

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				significant risks from intensive management of macrovascular and microvascular risks, or a short life expectancy are more likely to benefit from symptom management and strategies to improve quality of life
Pitfalls of using disease-specific guidelines for patients with multiple conditions (35)	USA	<p><i>Type of study/document:</i> Review (non-systematic)</p> <p><i>Methods used:</i> Not applicable</p>	Patients with multiple conditions	<p>20% of Medicare beneficiaries have five or more chronic conditions and 50% receive five or more medications.</p> <p>All medications have a potential for harm and benefit, and patients vary in regard to the amount of importance they place on health outcomes, the prevention of specific disease events, and the amount of inconvenience and risk of adverse effects they are willing to tolerate.</p> <p>Problems with using single-disease guidelines in the care of people with multiple conditions that were noted include:</p> <ul style="list-style-type: none"> - older patients and patients with multiple health conditions have been excluded from many randomized controlled trials (RCTs), and the generalizability of the results to these patients remains largely unknown; - adverse events are evaluated with less rigour and precision than are benefits in most RCTs; - drug recommendations for patients with multiple morbidities are presented but rarely prioritized; - many clinical trials supporting medication recommendation in guidelines are conducted over a few months or years which does not allow for the detection of benefit or harm from the use of the medicines for decades in the treatment of chronic conditions; - polypharmacy is associated with increased risk for adverse events <p>Recommendations for the improvement of guidelines include:</p> <ul style="list-style-type: none"> - transparent synthesis of evidence combined with collaboration and integration; - presentation of both benefits and harms based on absolute rather than relative scales and with measurements such as the number needed to treat (or harm), including, when data are available, sub-populations and follow-up times; - provision of priorities for prescribing medications for multiple conditions; and - integration of patient preferences should be included
Review on conflicting	Not applicable	<i>Type of study/document:</i> Comment/editorial	Not applicable	Clinical practice guidelines are increasingly being used for performance indicators, yet evidence-based diagnostic and treatment strategies generally overlook comorbidity,

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interests in comorbidity and guidelines (34)		<i>Methods used:</i> Not applicable		<p>which affects 25-50% of people with chronic diseases.</p> <p>Using disease-specific guidelines for patients with multimorbidities can introduce problems. Diagnosis and treatment can interact negatively with the treatment of a coexisting disease. Therefore, dealing with comorbidity needs a patient-centred rather than a disease-oriented approach.</p> <p>The authors divide comorbidities into four categories: causal, diseases with a common pathophysiology; complicating, disease-specific complicating morbidity; concurrent, coexisting chronic morbidity without any known causal relation to the index disease; and intercurrent, referring to interacting acute illness, usually limited in time. Causal or complicating diseases could be addressed by a single-disease guideline, but the guideline development would need to include patients with a mix of comorbid conditions included in randomized trials. Concurrent morbidity (e.g. frailty) makes management more complex and needs to be individualized.</p> <p>Recommendation: instead of trying to take all possible combinations of diseases into account in guidelines, emphasis should be placed on a holistic patient-centred approach, ensuring continuity of care and integrating the patients' biopsychosocial domains.</p>
Integrating multiple comorbidities in guideline development (37)	Canada	<p><i>Type of study/document:</i> Review (non-systematic)</p> <p><i>Methods used:</i> Searched PubMed and other databases of guidelines for existing systematic reviews and relevant research on the issue of guidelines, including COPD guidelines, and comorbidities. The authors also consulted references from their own files. Guidelines on major chronic diseases from international organizations were reviewed and examined to determine whether they addressed the issue of comorbidities in their guidelines.</p>	Not applicable	<p>Problems with using single-disease guidelines for people with multiple comorbidities that were highlighted include:</p> <ul style="list-style-type: none"> - the risk of undertreatment, overtreatment or inappropriate treatment, which can lead to increased costs, compromised adherence and increase the risk of adverse drug events; and - limited availability of evidence for people with multiple comorbidities outlined in guidelines <p>Recommended that guideline development panels should:</p> <ul style="list-style-type: none"> - aim for multidisciplinary representation, especially when developing recommendations for patients 65 years or older with multiple comorbidities; - evaluate the quality of evidence and the strength of recommendations targeted at this population; - add sections on addressing the impact of multiple comorbidities on screening, diagnosis, prevention and management of recommendations to existing COPD

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				<p>guidelines;</p> <ul style="list-style-type: none"> - use clarity in identifying which comorbidities were considered for recommendations within each guideline; - consider absolute risk reduction; - specify actual outcomes of each therapy (whether desired or undesired); - present the average and extremes of the length of therapy necessary to achieve risk reduction or symptom improvement; - address interactions that are common or important given the prevalence of specific comorbidities; - include patient preferences; and - include the feasibility of implementing guideline recommendations <p>Recommended that researchers should prioritize:</p> <ul style="list-style-type: none"> - assessing the effects of multiple concomitant medications and assess how their combined effects are altered by genetic, physiological, disease-related, and other factors; and - evaluating how these factors affect the applicability of the evidence for the target population
<p>Adapting clinical guidelines to account for multimorbidity (98)</p>	<p>U.K.</p>	<p><i>Type of study/ document:</i> Discussion paper (with literature review)</p> <p><i>Methods used:</i> Not applicable</p>	<p>Patients with multimorbidity</p>	<p>Problems of using single-disease guidelines for people with multimorbidity:</p> <ul style="list-style-type: none"> - combining recommendations for patients with multimorbidity can be harmful or burdensome; - polypharmacy can be associated with riskier prescribing and can be problematic in people who are physically frail or have cognitive impairment; and - benefit from treatment for those with limited life expectancy and recommendations for when chronic treatments should stop are not usually addressed <p>Recommendations provided to improve guidelines to better inform the treatment of people with multimorbidity include:</p> <ul style="list-style-type: none"> - cross-referencing guidelines using electronic delivery; - providing guidance about treatments most likely to benefit and least likely to harm (using absolute benefit when possible to account for an individual’s baseline risk of an outcome – number needed to treat (NNT)); and - making better use of existing evidence by including older people and those with multimorbidity in clinical trials, and use economic modelling, payoff time frameworks and structured expert elicitation methods (for uncertainty).

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<p>Developing clinical practice guidelines, part I of III: target audiences, identifying topics for guidelines, guideline group composition and functioning and conflicts of interest (93)</p>	<p>International</p>	<p><i>Type of study/document:</i> Methods development <i>Methods used:</i> Not applicable</p>	<p>Not applicable</p>	<p>There has been an emergence of guideline clearinghouses. And, methods of guideline development have progressed, so this and the next two papers update methods on developing clinical practice guidelines.</p> <p>1- Clarify the target audience, both primary (clinicians and patients for whom the guideline is intended and who are most likely to use the guideline) and secondary (professional organizations and policymakers) audiences. This helps inform decisions about the guideline’s scope, objectives, format and style of wording.</p> <p>2 – Prioritize topics for guideline development. Guidelines can be developed around conditions or procedures. These can be considered for guideline development when they are common, expensive, have effects on premature mortality or avoidable morbidity, there is evidence that medical care can make a difference in outcomes, and there are variations in practice, or practice does not meet some well-accepted standards.</p> <p>3 – Guideline development is both technical (systematic reviews of relevant evidence) and social (interpretations of the evidence and development of recommendations). Less attention has been given to the social component. Guideline groups should be multidisciplinary with representation from key stakeholder groups, but need to weigh wide representation and cohesiveness of working group. Usually 8-10 people are recommended for a working group, but larger groups can operate effectively. Guideline groups can also consider including consumers – patients and the public – into the guideline development process.</p> <p>4 – Guideline group processes should be addressed. Ideal conditions for group decision-making are those which enable the views of all parties to be expressed and considered before a recommendation is chosen that is acceptable to the majority. Group decision-making involves orientation (defining the problem), evaluation (discussion of decision alternatives), and control (deciding which alternative prevails).</p> <p>5 – Managing conflicts of interest, such as financial, intellectual and other investments in guideline development should be explicitly addressed. This includes having participants provide written disclosures of all potential conflicts of interests which should then be reviewed and managed prior to choosing participants for the guideline</p>

Document focus	Jurisdiction(s)	Type of study/document and methods used	Target population(s)	Key recommendations/findings
				group. Once the members are assembled, these potential conflicts of interest should be identified and discussed, and policies and procedures should be put in place to guide their management.
Developing clinical practice guidelines, part II of III: evidence and outcomes, values and economics, synthesis, grading, presentation and deriving recommendations (92)	International	<p><i>Type of study/document:</i> Methods development</p> <p><i>Methods used:</i> Not applicable</p>	Not applicable	<p>Principles for the development of a guideline include: making explicit decisions at the outset regarding the specific questions to be answered and the outcomes to be assessed, having a clear understanding of the analytic logic of the recommendations, using this model to keep the group’s work on track, being explicit about the types of evidence or opinions that support each component of the analytic logic, and transmitting this information to the reader in a clear way in the rationale statement of the guideline.</p> <p>The incorporation of values when the evidence is unclear or when subjective judgments of whether benefits outweigh harms, are neither right nor wrong, but should be transparent especially if recommendations are made in these situations.</p> <p>Available economic evidence may be limited in terms of general applicability to specific contexts of the clinical guideline, but it can help frame the general bounds of cost-effectiveness of management options for clinical conditions and provide sources for assumptions which may have to be made. This will be more difficult to incorporate in the setting of multiple morbidities.</p> <p>There is a fine balance between providing clear and precise guidance and not going beyond the supporting science.</p> <p>There have been more than 60 evidence grading systems used in the past. However, through selection of these instruments, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group approach has become one of the most common tools used. GRADE considers eight factors in the assessment of the quality of evidence for each important outcome.</p> <p>Concerns about study design and execution (risk of bias), consistency of the evidence across studies, directness of the evidence (generalizability, transferability and external validity), the precision of the estimate of effect, and publication bias can lower the confidence in an estimate of effect and study quality.</p> <p>On the other hand, three factors can increase the quality of evidence: a strong or very</p>

Identifying Optimal Treatment Approaches for People with Multimorbidity in Ontario

Document focus	Jurisdiction(s)	Type of study/document and methods used	Target population(s)	Key recommendations/findings
				<p>strong association, a dose-effect relationship, and all plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed.</p> <p>In addition, the overall quality of evidence is determined by the lowest quality of evidence for each of the critical outcomes. However, if the outcomes point to the same direction (e.g. benefit), then the overall quality of evidence reflects the quality of the better evidence.</p> <p>Four factors influence if a group makes a recommendation for or against a management strategy:</p> <ul style="list-style-type: none"> - the quality of the available body of evidence; - the magnitude of the differences between the benefits and undesirable downsides or harms; - the certainty about or variability in values and preferences of patients; and - the resource expenditure associated with the management option
<p>Developing clinical practice guidelines, part III of III: Discussion of the issues around reviewing, reporting and publishing guidelines for co-morbidity (94)</p>	<p>Not described in detail: U.K.</p>	<p><i>Type of study/ document:</i> Methods development</p> <p><i>Methods used:</i> Not applicable</p>	<p>Patients with co-morbidity</p>	<p>Guidelines should be updated at least every three years.</p> <p>One quarter of systematic reviews are likely out-of-date at two years post-publication.</p> <p>Situations that might necessitate the need to update clinical practice guidelines were identified as including changes in: the evidence on the existing benefits and harms of interventions; the outcomes considered important; the available interventions; the evidence that current practice is optimal; the values placed on outcomes; and resources available for healthcare.</p> <p>Strategies to support guidelines uptake were identified as including: pre-emptive identification of possible barriers of recommendations and a priori identification of solutions to address them; use of behaviourally specific language in the guidelines based on preferences of target group of healthcare practitioners, use of multiple formats and channels for guideline dissemination; targeted development of educational resources adapted in content; identifying resource implications of recommendations; and use of data collection tools.</p> <p>The concept of “concordant” (being ones that tend to have similar management</p>

Document focus	Jurisdiction(s)	Type of study/document and methods used	Target population(s)	Key recommendations/findings
				<p>plans) versus “discordant” comorbidities (ones with dissimilar management plans) might be helpful when developing clinical practice guidelines.</p> <p>Guidelines should include involving patients in discussions about their preferences for outcomes in order to weigh the risks and benefits of treatment.</p>
Developing international standards for clinical practice guidelines (96)	International	Consensus document. A literature review was conducted to identify critical components for high-quality guideline development. A consensus model was used to develop the document.	Not applicable	<p>Key components of high-quality and trustworthy guidelines include:</p> <ul style="list-style-type: none"> - a guideline development panel should include diverse and relevant stakeholders including health professionals, methodologists, topic experts and patients or other healthcare consumers; - a guideline should describe the process used to reach consensus among the panel members and approval by the sponsoring organization, when applicable, and this process should be determined before guideline development commences; - members of the guideline development group should disclose financial and nonfinancial conflicts of interest, and the guideline should describe how these conflicts were recorded and resolved; - the guideline’s objectives and scope should be specified; - the methods used for the development of the guideline should be described clearly; - guideline developers should utilize systematic review methods to identify and evaluate evidence related to the guideline topic; - guideline recommendations should be stated clearly and be based on scientific evidence of benefits, harms and costs, when possible; - the guideline should use a rating system to communicate the quality and reliability of the evidence and the strength of its recommendations; - the guideline should be reviewed by external stakeholders before publication; - an expiration date for the guideline and/or a process for updating the recommendations should be included; and - a guideline should disclose financial support for the development of the evidence review and the guideline recommendations.

Appendix 4: Excluded primary studies

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Appendix 5: Excluded guidelines

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