Current Guidelines Have Limited Applicability to Patients with Comorbid Conditions: A Systematic Analysis of Evidence-Based Guidelines

Marjolein Lugtenberg¹,²*, Jako S. Burgers²,³, Carolyn Clancy⁴, Gert P. Westert¹,², Eric C. Schneider⁵,⁶,⁷

¹ Scientific Centre for Care and Welfare (Tranzo), Tilburg University, Tilburg, The Netherlands, ² Scientific Institute for Quality of Healthcare (IQ Healthcare), Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, ³ Dutch College of General Practitioners (NHG), Utrecht, The Netherlands, ⁴ Agency for Healthcare Research and Quality (AHRQ), Rockville, Maryland, United States of America, ⁵ Harvard School of Public Health, Boston, Massachusetts, United States of America, ⁶ RAND Corporation, Boston, Massachusetts, United States of America, ⁷ Division of General Medicine and Primary Care, Brigham and Women’s Hospital, Boston, Massachusetts, United States of America

Abstract

**Background:** Guidelines traditionally focus on the diagnosis and treatment of single diseases. As almost half of the patients with a chronic disease have more than one disease, the applicability of guidelines may be limited. The aim of this study was to assess the extent that guidelines address comorbidity and to assess the supporting evidence of recommendations related to comorbidity.

**Methodology/Principal Findings:** We conducted a systematic analysis of evidence-based guidelines focusing on four highly prevalent chronic conditions with a high impact on quality of life: chronic obstructive pulmonary disease, depressive disorder, diabetes mellitus type 2, and osteoarthritis. 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). Of the 20 guidelines, 17 (85%) addressed the issue of comorbidity and 14 (70%) provided specific recommendations on comorbidity. In general, the guidelines included few recommendations on patients with comorbidity (mean 3 recommendations per guideline, range 0 to 26). Of the 59 comorbidity-related recommendations provided, 46 (78%) addressed concordant comorbidities, 8 (14%) discordant comorbidities, and for 5 (8%) the type of comorbidity was not specified. The strength of the supporting evidence was moderate for 25% (15/59) and low for 37% (22/59) of the recommendations. In addition, for 73% (43/59) of the recommendations the evidence was not adequately translated into the guidelines.

**Conclusions/Significance:** Our study showed that the applicability of current evidence-based guidelines to patients with comorbid conditions is limited. Most guidelines do not provide explicit guidance on treatment of patients with comorbidity, particularly for discordant combinations. Guidelines should be more explicit about the applicability of their recommendations to patients with comorbidity. Future clinical trials should also include patients with the most prevalent combinations of chronic conditions.

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* E-mail: m.lugtenberg@iq.umcn.nl

Introduction

Traditionally, medical care is focused on the prevention, diagnosis and treatment of single diseases [1]. Most research studies focus on the effectiveness of disease-specific interventions and patients with comorbidity or complex problems are often excluded from clinical trials [2,3]. In clinical practice, physicians are encouraged to adhere to evidence-based clinical practice guidelines (CPGs), as these are regarded as important tools for quality improvement [4]. In line with both clinical practice and research traditions, most CPGs are disease-oriented documents focusing on the diagnosis and management of single diseases [5].

The emphasis of CPGs on single diseases may be problematic. Almost half of patients with chronic diseases have more than one disease [6,7]. Managing multiple conditions is more complex than managing single diseases and clinicians may find it challenging to provide optimal care for patients with multiple conditions [8–10]. Particularly when conditions are discordant, i.e. if they are not directly related in either their pathogenesis or management and do not share an underlying predisposing factor, patients are more likely to report conflicting instructions and problems with coordination of care [11–13].

To the extent that CPGs focus on single diseases, they may offer insufficient guidance to physicians about care for patients with
multiple conditions. Lack of applicability of CPGs due to comorbidity may pose an important barrier to guideline adherence among physicians [14,15]. Moreover, adhering to single disease CPGs in caring for patients with multiple conditions may adversely affect patient safety, if recommended treatments for one condition conflict with those for another condition [16]. Although prior studies suggest that physicians may find it challenging to provide care to patients with comorbidity, there are few systematic assessments of the comorbidity-related content of CPGs, and in particular the quality of the evidence that supports that content. The aim of this study was to explore the applicability of CPGs to patients with comorbidity by assessing the extent to which CPGs on high-prevalence chronic conditions address comorbidity and by assessing the quality of the evidence cited in support of recommendations related to comorbidity.

Methods

Data sources

Two publicly-available international databases, the National Guideline Clearinghouse (NGC) and the Guidelines International Network Library (G-I-N), were used to select the guidelines.

Study selection

Selection of chronic conditions. In selecting the conditions, we focused on highly prevalent chronic diseases that have a high impact on quality of life. Both major depressive disorder [17,18] and diabetes mellitus type 2 [19,20] are highly prevalent and have been found to have a high impact on quality of life, particularly in combination [17,21]. We also included chronic obstructive pulmonary disease (COPD) and osteoarthritis, as pain and dyspnea may have a considerable impact on quality of life as well.

Selection of clinical practice guidelines

Guidelines were included if they:

- included a set of recommendations with an explicit link to their supporting evidence;
- were published in 2005 or later;
- addressed the treatment or management of the selected conditions;
- were published in English;
- were accessible in the public domain.

CPGs were excluded if they focused on a specific subgroup of patients (e.g. pregnant women, children, adolescents, homeless people).

Data extraction

One of the investigators (ML) abstracted data from the selected CPGs and the abstraction process was checked by a second investigator (JB). Any disagreement was resolved by discussion. General data were retrieved from the CPGs, and more detailed information was collected on the specific recommendations addressing comorbidity and their supporting evidence:

Guideline

- General characteristics of the guideline: title; organization; country; target group; year of publication; number of pages and references; number of treatment recommendations;
- Characteristics of the guideline related to comorbidity: issue of comorbidity addressed (prevalence data, screening/diagnosing for comorbidity; considering comorbidity in treatment);
- Contra-indications for medication or surgery were not considered as specific comorbidity-related recommendations, if no alternative treatments were provided.

Recommendation

- Type of recommendation: type of treatment addressed (general treatment, drug therapy, life-style advice, surgery, other); inclusion of patient-centered aspects.
- Number of comorbid conditions addressed;
- Type of comorbidity addressed: concordant or discordant. Concordant conditions were defined as representing the same overall pathophysiological risk profile and being more likely to be the focus of the same disease and self management plan [12]. Discordant treatments are not directly related in either their pathogenesis or management. For each of the included conditions the authors developed a scheme of concordant and discordant comorbidities (File S1). For diabetes, we did not consider cardiovascular risk factors such as hypertension and hyperlipidemia as concordant conditions but as part of the disease, because adequate management of diabetes is cardiovascular risk management including monitoring blood pressure and lipids.

Evidence

- Link with underlying evidence described; (yes, no)
- Number of underlying studies;
- Level of evidence of underlying studies: high, moderate, low, not available. As grading systems differ per guideline, we considered the highest level of evidence as high, the lowest level as low, and intermediate levels as moderate.
- Translation of evidence: good, moderate or poor/unclear. Our judgment was based on the directness of the evidence and on whether the strengths and limitations of the evidence were discussed in the guideline. The translation was graded as: ‘good’ if the supporting evidence of the studies focused (at least partly) on the comorbidity part of the recommendation and the strengths and limitations of the supporting evidence were discussed in the guideline; as ‘moderate’ if either the supporting evidence of the studies focused (at least partly) on the comorbidity part of the recommendation or the strengths and limitations of the supporting evidence were discussed in the guideline; and as ‘poor or unclear’ if neither the supporting evidence of the studies focused on the comorbidity part of the recommendation nor were the strengths and limitations of the supporting evidence discussed in the guideline.

Results

A total of 20 CPGs met our inclusion criteria, having been published in English and in the public domain since 2005 (Table 1). Six of the CPGs addressed COPD, four addressed major depressive disorder, seven addressed diabetes mellitus type 2 and three addressed osteoarthritis.

Eight CPGs were retrieved from the G-I-N database, six from the NGC database and six were available in both databases. The
The largest share of these 20 CPGs was produced in the United States (n = 7). Nine CPGs were produced by governmental agencies; five by professional societies and six by other types of organizations. The CPGs were predominantly developed in 2008 (7/20) and in 2007 (5/20).

Table 1. Basic characteristics of selected guidelines (N = 20).

| Title of guideline | Organization that developed guideline | Country | Year | No. of pages | No. of references |
|--------------------|---------------------------------------|---------|------|--------------|-------------------|
| COPD               |                                       |         |      |              |                   |
| 1. Chronic obstructive pulmonary disease | Singapore Ministry of Health | Singapore | 2006 | 84 | 155 |
| 2. Diagnosis and management of Chronic obstructive pulmonary disease (COPD) | Institute for Clinical Systems Improvement (ICSI) | USA | 2009 | 51 | 97 |
| 3. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians | American College of Physicians | USA | 2007 | 6 | 54 |
| 4. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease | Global Initiative for Chronic Obstructive Lung Disease - Disease Specific Society (WHO), National Heart, Lung, and Blood Institute (US.) | Several countries | 2008 | 94 | 435 |
| 5. Australian Lung Foundation & The Thoracic Society of Australia and New Zealand - The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2006 | New Zealand Guidelines Group (NZGG) | New Zealand | 2006 | 66 | 243 |
| 6. Canadian Thoracic Society Recommendations for Management of Chronic Obstructive Pulmonary Disease, CTS (CA) | Canadian Thoracic Society | Canada | 2007 | 28 | 366 |
| DEPRESSIVE DISORDER (MAJOR) |                                       |         |      |              |                   |
| 7. Major depression in adults in primary care | Institute for Clinical Systems Improvement (ICSI) | USA | 2008 | 84 | 244 |
| 8. Identification of common mental disorders and management of depression in primary care | New Zealand Guidelines Group (NZGG) | New Zealand | 2008 | 188 | 580 |
| 9. Using Second-Generation Antidepressants to Treat Depressive Disorders: A Clinical Practice Guideline from the American College of Physicians | American College of Physicians (ACP) | USA | 2008 | 10 | 100 |
| 10. A. Depression: the treatment and management of depression in adults (update) (CG90) | National Institute for Health and Clinical Excellence (NICE) | United Kingdom | 2009 | 64 (FG = 585) | 0 (FG > 1000) |
| DIABETES MELLITUS TYPE 2 |                                       |         |      |              |                   |
| 11. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus | American Association of Clinical Endocrinologists, American College of Endocrinology | USA | 2007 | 68 | 564 |
| 12. Diabetes mellitus | Singapore Ministry of Health | Singapore | 2006 | 161 | 260 |
| 13. Diagnosis and management of type 2 diabetes mellitus in adults | Institute for Clinical Systems Improvement (ICSI) | USA | 2008 | 89 | 126 |
| 14. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases | European Society of Cardiology | Several European countries | 2007 | 72 | 711 |
| 15. Standards of medical care in diabetes | American Diabetes Association | USA | 2008 | 43 | 332 |
| 16. National evidence-based guidelines for type 2 diabetes mellitus (Part 1, 3, 4, 5 & 7) | National Health and Medical Research Council (NHMRC) | Australia | 2005 | 928 | > 1000 |
| 17. Type 2 diabetes - the management of type 2 diabetes (partial update)+newer agents (CG87) | National Institute for Health and Clinical Excellence (NICE) | United Kingdom | 2009 | 151 (FG = 259) | 0 (FG = 414) |
| OSTEOARTHRITIS |                                       |         |      |              |                   |
| 18. Osteoarthritis of the knees | Singapore Ministry of Health | Singapore | 2007 | 51 | 91 |
| 19. The care and management of osteoarthritis in adults | National Institute for Health and Clinical Excellence (NICE) | United Kingdom | 2008 | 22 (FG = 316) | 0 (FG = 386) |
| 20. Ottawa Panel evidence-based clinical practice guidelines for therapeutic exercises and manual therapy in the management of osteoarthritis | Ottawa Panel | Canada | 2005 | 65 | 178 |

FG = Full guideline.
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Applicability of guidelines to patients with comorbidity

Of the 20 guidelines, 17 (85%) addressed the issue of comorbidity (Table 2). Eight guidelines (40%) provided comorbidity prevalence data, 16 guidelines (80%) recommended screening for comorbid conditions and 17 guidelines (85%)
recommended considering comorbidity in treatment. Guidelines on depressive disorder and diabetes mellitus type 2 (100%) more often addressed the issue of comorbidity compared to the guidelines on COPD (83%) and osteoarthritis (33%).

Fourteen (70%) guidelines provided specific treatment recommendations for patients with comorbid conditions. The number of recommendations varied from 1 to 26 per guideline, with an average of 3 per guideline. The guidelines on COPD and osteoarthritis provided the fewest numbers of recommendations (0.7 per guideline), whereas the guidelines on diabetes mellitus type 2 included an average of 6.3 comorbidity-related recommendations.

The 20 guidelines provided a total of 59 comorbidity-related treatment recommendations (Table 3). Seventy-eight percent (46/59) of these recommendations addressed concordant comorbidities. Most of the diabetes mellitus type 2 guideline recommendations addressed concordant comorbidities such as coronary artery disease and heart failure. Relative to the other guidelines, the guidelines on depressive disorder included the largest proportion (33%) of recommendations on discordant comorbidities (such as cardiovascular disease). More than 90% of the recommendations were related to one comorbid condition; 10% focused on comorbidities in general and none of the recommendations specified the management of patients with more than one comorbid condition.

Fifty-four percent of the comorbidity-related recommendations concerned drug therapy (32/59); 25% related to other types of treatment such as psychotherapy or oxygen therapy (15/59). Few recommendations focused on surgery (10%; 6/59) and on lifestyle advice (3%; 2/59). Twelve percent of the recommendations (7/59) provided specific guidance on patient-centered aspects such as patient preferences, burden of disease and priority setting.

The link between guideline recommendation statements and the supporting evidence was described for 97% of the recommendations (57/59). The number of underlying studies varied between 1 and 12 per recommendation. The level of evidence of the studies was generally weak: 37% of the recommendations (22/59) had a ‘low’ level of evidence; for 25% of the recommendations (15/59) the level of evidence was described as ‘moderate’ (Table 4 and 5).

For 73% of the recommendations (43/59), the evidence underlying the studies was not adequately translated into the guideline with 48% (29/59) graded as ‘moderate’ and 25% (15/59) as ‘poor or unclear’ (Table 4 and 5). Translation of evidence was rated more frequently as ‘good’ for guidelines on diabetes mellitus type 2 (32% [14/44]) than those on depression (22% [2/9]); none of the guidelines on COPD and osteoarthritis received a ‘good’ rating for evidence translation (Table 4).

Discussion

Patients with multiple comorbid conditions are very frequently encountered in clinical practice. However, our results suggest that evidence-based guidelines on four relatively prevalent chronic diseases may have limited applicability to patients with comorbid conditions. Most of these guidelines do not provide explicit guidance on treatment of patients with specific combinations of diseases. If comorbidity is addressed in the guidelines, it is often discussed in general; few specific treatment recommendations for patients with comorbid conditions are provided, particularly for discordant combinations. Moreover, the evidence supporting the available comorbidity-related recommendations was generally limited, had moderate to poor quality, and was often not adequately translated into the guidelines.

Among the guidelines in our study that included specific comorbidity-related recommendations, these recommendations were more likely to focus on concordant comorbidities with related treatment plans. We also found that none of the comorbidity-related recommendations specified the preferred action for patients with more than one concurrent condition. These results are consistent with previous American [16] and Australian [23] studies showing that guidelines pay little attention to patients with discordant comorbidities and to patients with multiple chronic conditions. This lack of attention contributes to limiting the applicability of single disease guidelines on patients with chronic diseases as almost one third of them have three or more conditions [24].

An important finding of our study is the limited evidence base that supports comorbidity-related recommendations. If specific recommendations for patients with comorbidity are provided, they are often based on limited evidence that is of moderate or poor quality. In addition, the supporting evidence rarely focuses directly on the groups of patients with comorbid conditions. Furthermore, the limitations of this evidence are not usually described in the guidelines. The failure to describe limitations of evidence in a guideline could give clinicians misplaced confidence in guideline recommendations.

Consistent with previous studies, our findings indicate that the evidence base for patients with multiple chronic conditions is limited [2,3]. The lack of evidence specific to comorbid conditions may explain the limited attention to comorbidity in the guidelines we studied. If future clinical trials included patients with comorbidity...
conditions, at least for the most common combination of diseases and report the results, this would provide the evidence base that clinical guideline developers need [16,25].

In light of the general absence of research evidence on patients with multiple conditions, guidelines should be more explicit about the applicability of their recommendations to patients with the most prevalent comorbid conditions and discuss the quality and directness of the evidence for these patients. This explicit approach should replace the implicit assumption that guideline recommendations are applicable to patients with comorbid conditions unless conflicting evidence is available [26,27].

Our findings indicate that no systematic approach is used by guideline development groups for addressing comorbidity in guidelines. Compared to the guidelines on COPD, depressive disorder, and osteoarthritis, the guidelines on diabetes mellitus type 2 had better reporting of issues of comorbidity. Even for guidelines on the same condition, we found large variation between guidelines in the approach to addressing comorbidity.

Table 3. Characteristics of comorbidity-related treatment recommendations (N = 59).

| Comorbidity-related treatment recommendations | COPD (N = 4) | DEP (N = 9) | DM II (N = 44) | OA (N = 2) | TOTAL (N = 59) |
|---------------------------------------------|-------------|-------------|----------------|-----------|----------------|
| N                                           | N           | N           | N              | N         | N%             |
| Type of comorbidity addressed                |             |             |                |           |                |
| concordant comorbidity                       | 3           | 5           | 38             | 0         | 46             | 78             |
| discordant comorbidity                       | 1           | 3           | 4              | 0         | 8              | 14             |
| not specified                                | 0           | 1           | 2              | 2         | 5              | 8              |
| Nr of comorbid conditions addressed          |             |             |                |           |                |
| one comorbid condition                       | 4           | 8           | 42             | 0         | 54             | 92             |
| multiple comorbidities                       | 0           | 0           | 0              | 0         | 0              | 0              |
| not specified                                | 0           | 1           | 2              | 2         | 5              | 8              |
| Type of recommendation                       |             |             |                |           |                |
| general treatment                            | 0           | 3           | 1              | 0         | 4              | 7              |
| drug therapy                                 | 1           | 4           | 27             | 0         | 32             | 54             |
| life-style advice                            | 0           | 0           | 1              | 1         | 2              | 3              |
| surgery                                      | 0           | 0           | 5              | 1         | 6              | 10             |
| other*                                       | 3           | 2           | 10             | 0         | 15             | 25             |
| Includes patient centered aspects            | 0           | 3           | 4              | 0         | 7              | 12             |

COPD = Chronic Obstructive Pulmonary Disease; DEP = Major depressive disorder; DM II = Diabetes Mellitus type 2; OA = Osteoarthritis.
*The category 'other' includes: psychological interventions, oxygen therapy, referral, assessment before flying, target levels, risk stratification.

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Table 4. Evidence-base of comorbidity-related treatment recommendations (N = 59).

| Comorbidity-related treatment recommendations | COPD (N = 4) | DEP (N = 9) | DM II (N = 44) | OA (N = 2) | TOTAL (N = 59) |
|---------------------------------------------|-------------|-------------|----------------|-----------|----------------|
| N                                           | N           | N           | N              | N         | N%             |
| Number of underlying studies                |             |             |                |           |                |
| 0 or unclear                                | 1           | 1           | 7              | 1         | 10             | 17             |
| 1–2                                         | 3           | 4           | 12             | 0         | 19             | 32             |
| 3–4                                         | 0           | 3           | 11             | 0         | 14             | 24             |
| >4                                          | 0           | 0           | 5              | 1         | 6              | 10             |
| Level of evidence of the studies            |             |             |                |           |                |
| high                                        | 2           | 0           | 14             | 0         | 16             | 27             |
| moderate                                    | 1           | 2           | 12             | 0         | 15             | 25             |
| low                                         | 1           | 5           | 16             | 0         | 22             | 37             |
| N.A.                                        | 0           | 2           | 2              | 2         | 6              | 10             |
| Translation of evidence                     |             |             |                |           |                |
| good                                        | 0           | 2           | 14             | 0         | 16             | 27             |
| moderate                                    | 3           | 3           | 22             | 0         | 28             | 48             |
| poor or unclear                             | 1           | 4           | 8              | 2         | 15             | 25             |

COPD = Chronic Obstructive Pulmonary Disease; DEP = Major depressive disorder; DM II = Diabetes Mellitus type 2; OA = Osteoarthritis.
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This applies to all levels of abstraction (guideline, recommendation, evidence). A previous study comparing diabetes guidelines from different countries, also found much variation in the supporting evidence, whereas the recommendations were similar [28]. It would be helpful to develop guidance, as part of a handbook or manual for guideline developers [29,30] to facilitate supporting evidence, whereas the recommendations were similar [28]. It would be helpful to develop guidance, as part of a handbook or manual for guideline developers [29,30] to facilitate supporting evidence, whereas the recommendations were similar [28]. It would be helpful to develop guidance, as part of a handbook or manual for guideline developers [29,30] to facilitate supporting evidence, whereas the recommendations were similar [28]. It would be helpful to develop guidance, as part of a handbook or manual for guideline developers [29,30] to facilitate supporting evidence, whereas the recommendations were similar [28]. It would be helpful to develop guidance, as part of a handbook or manual for guideline developers [29,30] to facilitate supporting evidence, whereas the recommendations were similar [28]. It would be helpful to develop guidance, as part of a handbook or manual for guideline developers [29,30] to facilitate supporting evidence, whereas the recommendations were similar [28]. It would be helpful to develop guidance, as part of a handbook or manual for guideline developers [29,30] to facilitate supporting evidence, whereas the recommendations were similar [28]. It would be helpful to develop guidance, as part of a handbook or manual for guideline developers [29,30] to facilitate supporting evidence, whereas the recommendations were similar [28]. It would be helpful to develop guidance, as part of a handbook or manual for guideline developers [29,30] to facilitate supporting evidence, whereas the recommendations were similar [28]. It would be helpful to develop guidance, as part of a handbook or manual for guideline developers [29,30] to facilitate supporting evidence, whereas the recommendations were similar [28]. It would be helpful to develop guidance, as part of a handbook or manual for guideline developers [29,30] to facilitate supporting evidence, whereas the recommendations were similar [28].
comorbid conditions and it is rare that guidelines adequately describe the limitations of the evidence. Given the increasing prevalence of patients with multiple chronic diseases, guidelines should at least be explicit and transparent about the applicability of their recommendations to populations of patients with the most common combination of diseases. A guide for guideline developers could facilitate a systematic and uniform approach.

Supporting Information

File S1 Classification of concordant and discordant comorbidities.

(DOC)

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Author Contributions

Conceived and designed the experiments: MI, JB CC GW ES. Analyzed the data: MI, JB. Wrote the paper: MI, JB CC GW ES.

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