

Draft Comparative Effectiveness Review

Number XX

**Practice-Based Interventions Addressing Concomitant
Mental Health and Chronic Medical Conditions in the
Primary Care Setting**

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see <http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm>

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (<http://www.effectivehealthcare.ahrq.gov>) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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The investigators deeply appreciate the considerable support, commitment, and contributions of the EPC team staff at XXX. We express our gratitude to the following individuals for their contributions to this project: <NAME, degrees>

Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

Key Informants

To be completed after peer review.

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Technical Experts comprise a multidisciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism

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Technical Expert Panel

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Practice-Based Interventions Addressing Concomitant Mental Health and Chronic Medical Conditions in the Primary Care Setting

Structured Abstract

Objectives: To assess the effectiveness of practice-based interventions in improving outcomes for concomitant mental health and chronic medical conditions in the primary care setting.

Data Sources: We searched MEDLINE[®], Embase, the Cochrane Library, CINAHL[®], and PsycINFO[®] from inception to May 2011. We identified additional studies from reference lists and technical experts.

Review Methods: Two people independently selected, extracted data from, and rated the quality of relevant trials and systematic reviews. We conducted quantitative analyses for outcomes when feasible and reported all results by medical condition when possible. Two reviewers graded the strength of evidence (SOE) using established criteria.

Results: We included 19 published articles reporting data from 10 randomized controlled trials. Sample sizes ranged from 55 to 1,001, and study duration ranged from 6 to 24 months. Nine trials were conducted in the United States (1 in Puerto Rico) and 1 in Scotland. All trials characterized their respective intervention as a form of collaborative care and generally involved a care manager with physician supervision; we found no studies describing other types of practice-based interventions. Settings of care for included trials, although rarely characterized, included both open and closed systems. All trials specified depression as the targeted mental health condition; none targeted anxiety. Medical conditions included arthritis, cancer, diabetes, heart disease, HIV, and one or more conditions. Our meta-analyses found that intervention recipients achieved greater improvement than controls in depression symptoms, response, remission, and depression-free days (*moderate* SOE); satisfaction with care (*moderate* SOE); and mental and physical quality of life (*moderate* SOE). Few data were available on outcomes for chronic medical conditions except for diabetes; only 1 trial used a medical outcome as the primary outcome. Diabetics receiving collaborative care had greater adherence to some aspects of self-care (*low* SOE) but exhibited no difference in hemoglobin (Hb) A1c compared with diabetics in control groups (weighted mean difference 0.13, 95% CI -0.55 to 0.41 at 6 months; 0.24, 95% CI -0.14 to 0.62 at 12 months; *low* SOE).

Conclusions: Collaborative care interventions improved outcomes for depression and quality of life in primary care patients with multiple different medical conditions. Future studies should target a broader range of specific medical conditions, or clusters of conditions, and should compare variations of practice-based interventions to examine determinants of effectiveness.

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Executive Summary

Background

The World Health Organization has identified the integration of mental health into primary care as the most salient means of addressing the burden of mental health conditions, noting its “urgent importance.”¹ In the United States, half of the care for common mental health disorders is delivered in general medical settings,² emphasizing the vital role that primary care providers play in the diagnosis and treatment of these disorders.

Common mental health conditions, such as depression and anxiety, are found in up to 10 percent of primary care patients,³ and these conditions often coexist with chronic medical conditions. Accordingly, considerable interest has been expressed in improving the recognition and management of mental health conditions, especially depression, within primary care.⁴⁻⁶ Specifically, interest is emerging about whether treatment of common mental health conditions in primary care can improve both mental health and chronic medical outcomes. The arena of mental health and primary care is moving from consideration of single conditions and their outcomes to more real-world, complex-care paradigms.^{2,7} However, to date, no synthesis of the evidence has been done in a way that accounts for the primary care patient with “multiple chronic conditions”⁸ and examines both mental health and chronic medical outcomes simultaneously.

Mental Health Conditions

According to the National Comorbidity Survey Replication, 12-month prevalence of any mental health disorder in the United States is 26.2 percent; more than half of these cases (14.4 percent) meet criteria for only one disorder, and smaller proportions meet criteria for two (5.9 percent) or more disorders (5.9 percent).⁹ Of the mental health conditions, depression and anxiety cause the greatest societal burden as measured by social and economic costs.¹⁰ Indeed, by 2030, depression itself is projected to be the single leading cause of overall disease burden in high-income countries.¹¹ Worldwide, depression makes a large contribution to the burden of disease, ranking third worldwide, eighth in low-income countries, and first in middle- and high-income countries.¹² In 2000, the U.S. economic burden of depressive disorders was estimated to be \$83.1 billion.¹³ More than 30 percent of these costs are attributable to direct medical expenses.¹³ The economic burden of anxiety disorders is similarly high, with cost estimates reaching \$54.9 billion per year.¹⁴

Chronic Medical Conditions

Half of all Americans live with a chronic medical condition.¹⁵ An estimated 23.6 million people (7.8 percent of the U.S. population) have diabetes.¹⁶ Roughly 24 million U.S. adults have chronic obstructive pulmonary disease, and an additional 23 million have asthma.¹⁷ Up to one-quarter of people living with chronic medical conditions have limitations in daily activity.¹⁵ Living with chronic disease also takes a personal and emotional toll on patients and their families, owing to significant reductions in quality of life.¹⁵

Concomitant Mental Health and Chronic Medical Conditions

Chronic medical conditions commonly associated with depression (Table ES-1) and/or anxiety include arthritis, heart disease, diabetes, asthma, lung disease, and cancer.^{18, 19} Depression among people with chronic physical illness has been linked to an increase in health care utilization, disability, and work absenteeism when compared with those without depression, even after controlling for the varying burden of the physical health condition.²⁰ In one study of primary care outpatients with hypertension, diabetes, and/or heart disease, between 26 percent and 28 percent of patients reported a diagnosis of anxiety disorder at some point in their lives.²¹

Table ES-1. Prevalence of depression in chronic medical conditions

Chronic Condition	Prevalence of Depression
Arthritis	
Rheumatoid arthritis	13%-20% ^{22, 23}
Osteoarthritis	19.4% ²⁴
Heart disease	
Post-myocardial infarction	10%-47% ²⁵
Coronary artery disease	15% ²⁶ -23% ²⁷
Diabetes	11%-15% ²⁸ (MDD specifically) 17.6% ²⁹ -31.0% ²⁸ (any depressive disorder)
Pulmonary disease	
Asthma	26.6% ³⁰
Chronic obstructive pulmonary disease	27.2% ³¹
Cancer	9%-24% ³² (MDD) 20%-50% ³² (any depressive disorder)

Abbreviations: MDD, major depressive disorder

Treating Mental Health Conditions in Primary Care

Strategies addressing the management of mental health conditions in primary care have focused on depression. Repeated evidence reviews show the benefits of integrated and collaborative care models, as compared with usual care, on the outcomes of depression in the general health setting.^{4, 33-35} Literature on the treatment of other mental health conditions such as anxiety in primary care is less mature, but data suggest that such conditions may also be successfully treated in primary care.³⁶ Further, an emerging literature addresses whether better treatment of depression in primary care can also improve chronic medical outcomes, such as for diabetes.³⁷⁻³⁹ A review of similar studies will help address the clinical uncertainty about whether such collaborative interventions can make a difference in more than one disease outcome and inform policy decisions about the potential benefit of adopting such guidance.

Scope and Key Questions

Scope of the Review

This review summarizes the body of evidence that examines the effectiveness of practice-based interventions targeting primary care patients with both depression or anxiety and a chronic medical condition(s). Narrowing the scope in this way selects for a population with known burden and associated higher risk for poor outcomes, and doing so can help answer the uncertainty about whether such focused efforts can improve more than one condition at a time. In an effort to address the inherent heterogeneity of complex interventions,⁴⁰ this report also compares the specific characteristics of the interventions and the practice settings in which they are delivered.

These results should be of interest to multiple stakeholders, including patients, providers, and policymakers. A family physician nominated this topic because he wanted to know whether concomitantly treating mental health and general health conditions in the primary care setting could improve overall health outcomes and prevent the fragmentation of services across providers. As we move to consider shared savings programs, such as accountable care organizations,⁴¹ and the patient-centered medical home,⁴¹ consumers and payers are eager to identify interventions and processes that can streamline care for multiple conditions and improve the quality and efficiency of care. Interestingly, numerous barriers, many financial, hinder implementation of collaborative depression treatment in primary care despite its considerable evidence base.^{4, 42, 43} This report aims to provide new data about the common and costly problem of primary care patients with concomitant mental health and chronic medical conditions. Such information can inform clinical decisionmaking as well as potential reimbursement and coverage strategies.

As we conceptualized the approach to this report, preliminary evidence reviews revealed that data were insufficient on mental health conditions other than depression and anxiety that met our eligibility criteria. To reduce confusion regarding the universe of potential mental health conditions, therefore, the remainder of this report focuses on depression and anxiety.

Population

The main focus of this review is adults with one or more diagnosed chronic medical conditions and a diagnosis of either depression or anxiety (or both) that are being treated in a primary care setting. An example is patients with diabetes and depression. The purpose is to include patients with a level of severity known to benefit from treatment and to be associated with poor outcomes. Settings include traditional primary care (e.g., family medicine, internal medicine, obstetrics/gynecology, and geriatrics) and settings with a primary care–type relationship (e.g., oncology clinics for those with cancer, infectious disease clinics for those with HIV).

Interventions

For this review we use the term *practice-based* to define the interventions of interest. This term reflects an explicit effort to be inclusive of a wide range of interventions while also requiring the primary care site to be the nucleus of activity. Our rationale is to honor the spirit of the original nomination by acknowledging the crucial role of primary care, where most patients receive care, and from which care is optimally coordinated.⁴⁴

Practice-based is understood to mean any intervention that (1) targets the *care process* within a system of care and (2) aims to improve the mental health condition or both the mental health and chronic medical conditions. Examples of practice-based interventions include but are not limited to coordinated care, integrated care, and collaborative care; they often involve a care manager. Because of the dual focus on (1) concurrent management of both the mental health and the chronic medical condition within primary care and (2) systematic changes that can improve the delivery of care (rather than testing specific interventions), we exclude medication-only, device, and psychotherapy-only clinical trials (e.g., efficacy studies comparing a medication with a placebo) from this review. Practice-based interventions can include person-level components such as problem-solving therapy and antidepressant medications, but they must be delivered as part of a broader systematic strategy to improve care.

Key Questions

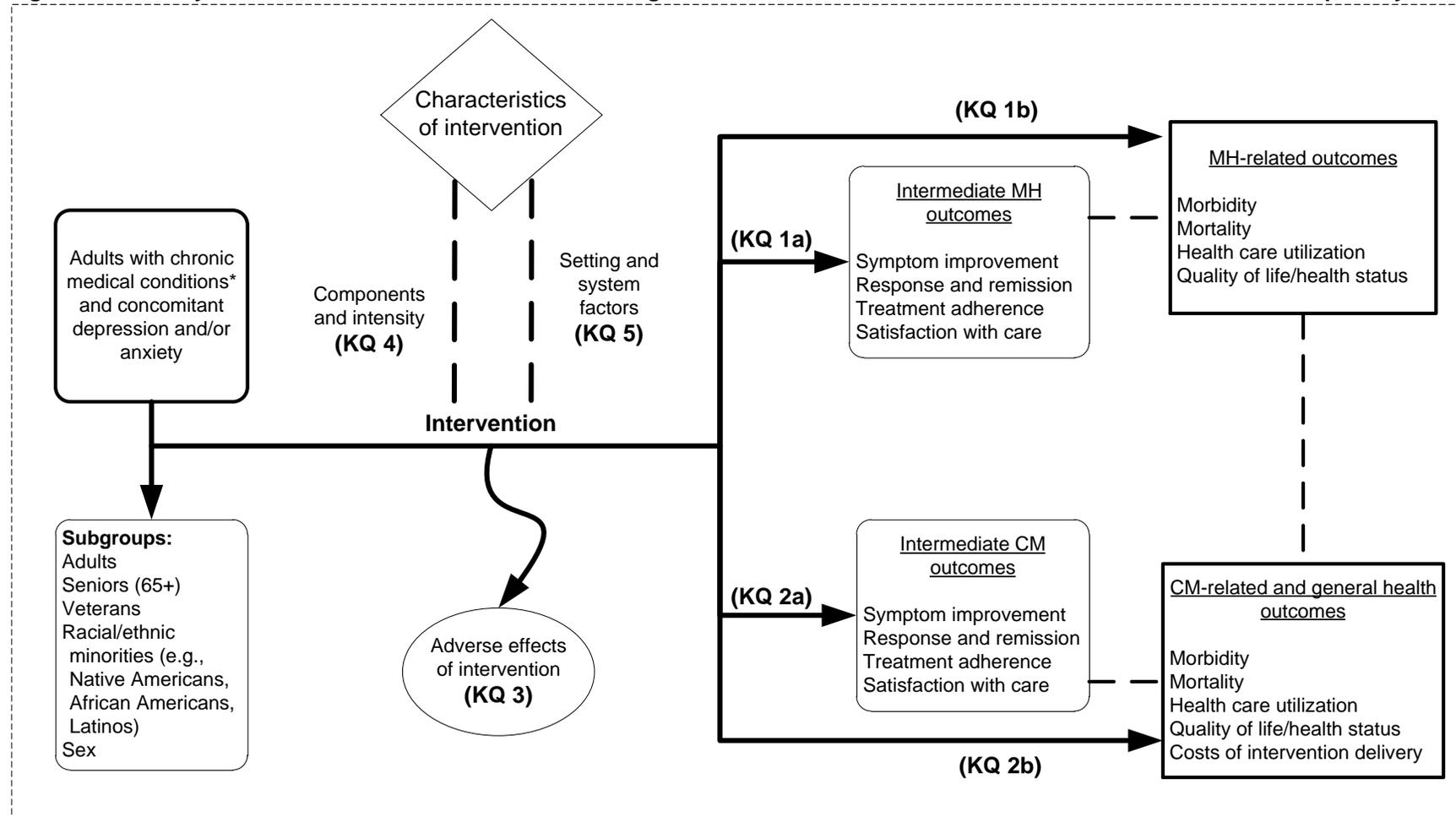
- Key Question (KQ) 1a: Among adults with chronic medical conditions and concomitant depression and/or anxiety (such as patients with diabetes and depression) treated in the primary care setting, what is the comparative effectiveness of practice-based interventions aimed at improving the mental health condition or both the mental health and chronic medical conditions (when compared with similar interventions or usual care) *on intermediate depression/anxiety outcomes (e.g., symptom improvement)*?
- KQ 1b: Among adults with chronic medical conditions and concomitant depression and/or anxiety (such as patients with diabetes and depression) treated in the primary care setting, what is the comparative effectiveness of practice-based interventions aimed at improving the mental health condition or both the mental health and chronic medical conditions (when compared with similar interventions or usual care) *on other mental health outcomes (e.g., depression-related quality of life) and mental health-related utilization*?
- KQ 2a: Among adults with chronic medical conditions and concomitant depression and/or anxiety (such as patients with diabetes and depression) treated in the primary care setting, what is the comparative effectiveness of practice-based interventions aimed at improving the mental health condition or both the mental health and chronic medical conditions (when compared with similar interventions or usual care) *on intermediate chronic medical outcomes (e.g., hemoglobin [Hb]A1c for patients with diabetes)*?
- KQ 2b: Among adults with chronic medical conditions and concomitant depression and/or anxiety (such as patients with diabetes and depression) treated in the primary care setting, what is the comparative effectiveness of practice-based interventions aimed at improving the mental health or both the mental health and chronic medical conditions (when compared with similar interventions or usual care) *on general health outcomes (e.g., diabetes-related morbidity)*?
- KQ 3: What harms are associated with practice-based interventions for primary care patients with chronic medical conditions and concomitant depression and/or anxiety?
- KQ 4: What are the characteristics of the practice-based interventions addressing concomitant mental health and chronic medical conditions used in the primary care setting with regard to specific components and/or intensity (e.g., visit frequency, total number of contacts, provider discipline, use of self-management)?
- KQ 5: What are the specific characteristics of the practice setting where the interventions were delivered with regard to such variables as organizational characteristics (e.g., decision support, level of integration, information technology, electronic medical records, presence of mental health services on site, payer and service mix, practice size, and practice location/setting) or the relationship between elements of the system in which the practice operates (e.g., coordination, financing of care, payment arrangements).

Analytic Framework

We developed an analytic framework to guide the systematic review process (Figure ES-1). KQ 1 addresses the effectiveness of practice-based interventions for improving mental health outcomes: 1a addresses intermediate clinical outcomes related to mental health, such as symptom response, and 1b addresses other outcomes related to mental health, such as depression-related quality of life, and mental health care utilization. KQ 2 addresses the effectiveness of practice-based interventions for improving chronic medical condition outcomes: KQ 2a addresses

Figure ES-1. Analytic framework for interventions addressing concomitant mental health and chronic medical conditions in primary care

ES-5



* Chronic medical conditions are considered broadly and include the AHRQ priority conditions and IOM priority conditions, such as diabetes, arthritis, and chronic pain, among others.

Abbreviations: CM, chronic medical; MH, mental health interventions.

intermediate clinical outcomes, such as pain severity scores for patients with arthritis, and 2b addresses other important chronic medical outcomes, such as disease-related quality of life, and general health-related utilization. KQ 3 addresses the potential harms of practice-based interventions. KQs 4 and 5 assess the characteristics of the interventions and practice settings, respectively.

Methods

Topic Refinement and Review Protocol

During the topic development and refinement processes, we generated an analytic framework, preliminary Key Questions, and preliminary inclusion/exclusion criteria in the form of PICOTS (Population, Intervention, Comparison, Outcome, Timing, and Setting). We worked with five Key Informants during the topic refinement and seven members of our Technical Expert Panel during the comparative effectiveness review process; they provided input on the scope, process, and reporting methods of the review.

To achieve an appropriate scope for the review, we prioritized conditions and interventions that were most clinically relevant. Specifically, we selected the mental health conditions most commonly encountered by primary care providers (depression and anxiety) and the following chronic medical conditions identified as priority conditions by the Agency for Healthcare Research and Quality (AHRQ)⁴⁵ and the Institute of Medicine:⁴⁶ arthritis; diabetes; asthma or chronic obstructive pulmonary disease (COPD); cancer; chronic pain; stroke; HIV/AIDS; heart disease, heart failure, myocardial ischemia, coronary artery bypass graft, postmyocardial infarction, and coronary artery disease; “complex” patients with multiple comorbidities; and frailty due to old age.

Literature Search Strategy

We searched MEDLINE[®], Embase, the Cochrane Library, CINAHL[®], and PsycINFO[®] from the inception of each database through May 23, 2011. We used Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate, focusing on terms to describe the relevant population and the interventions of interest. We reviewed our search strategy with the Technical Expert Panel members and incorporated their input into our search strategy. We limited the electronic searches to English language. The final search strategy is listed in Appendix A.¹ We manually searched reference lists of pertinent reviews, included trials, and background articles on this topic to look for any relevant citations that might have been missed by our searches.

We developed eligibility (inclusion and exclusion) criteria with respect to patient PICOTS, and study designs and durations for each part of KQs 1 and 2. We included controlled studies of at least 6 months’ duration in adults (age 18 or older) with depression and/or anxiety and one or more of the chronic medical conditions listed above. We also searched for systematic reviews of such studies.

Depression and anxiety were defined as threshold-level conditions, meeting criteria for a disorder as determined by valid and reliable measures with established cutpoints; we excluded subthreshold symptoms and minor depression. Included studies must have used practice-based

¹ Appendixes referenced in this Executive Summary are the same as those referenced in the main report. Please see main report for complete appendixes.

interventions aimed at improving the mental health condition or both the mental health and chronic medical conditions. A practice-based intervention is one that targets the *care process* within a system of care. Examples of practice-based interventions include coordinated care, integrated care, and collaborative care. Eligible controls were other practice-based interventions or usual care. All studies eligible for KQ 1 or 2 were eligible for KQs 3, 4, and 5.

All titles and abstracts identified through searches were independently reviewed by two trained members of the research team. Studies marked for possible inclusion by either reviewer were retrieved for full-text review. Each full-text article retrieved was independently reviewed by two trained members of the team for final inclusion/exclusion. If the reviewers disagreed, conflicts were resolved by discussion with an experienced team member.

For studies that met our inclusion criteria, we abstracted important information into evidence tables. We designed structured data abstraction forms to gather pertinent information from each article. Trained reviewers extracted the relevant data from each included article into the evidence tables. A second member of the team reviewed all data abstractions for completeness and accuracy.

Quality Assessment of Individual Studies

To assess the quality (internal validity) of studies, we used predefined criteria based on those developed by the U.S. Preventive Services Task Force (USPSTF) (ratings: good, fair, poor)⁴⁷ and the University of York Centre for Reviews and Dissemination.⁴⁸ In general terms, a “good” study has the least risk of bias and its results are considered to be valid. A “fair” study is susceptible to some bias but probably not sufficient to invalidate its results. A “poor” study has significant risk of bias (e.g., stemming from serious errors in design or analysis) that may invalidate its results.

Two independent reviewers assigned quality ratings for each study. Disagreements between the two reviewers were resolved by discussion and consensus or by consulting a third member of the team. We excluded studies rated “poor” from our analyses.

Data Synthesis

The research team determined prioritization and/or categorization of outcomes with input from Technical Expert Panel members. With their participation, we decided that despite the variation and inherent heterogeneity of medical conditions, we would analyze outcomes across conditions to provide a summary effect. We conducted quantitative analyses using meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough for us to justify combining their results. When quantitative analyses were not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we synthesized the data qualitatively.

Random-effects models were used to estimate pooled effects.⁴⁹ For continuous outcomes, we used the weighted mean difference as the effect measure; if the measurement scale differed among trials, we calculated the standardized mean difference. For most dichotomous outcomes, we report risk differences. Sensitivity analyses were conducted for all analyses where considerable heterogeneity was present (i.e., I^2 statistic greater than 75 percent).

Strength of the Body of Evidence

We graded the strength of evidence based on the guidance established for the Evidence-based Practice Center Program.⁵⁰ Developed to grade the overall strength of a body of evidence, this

approach incorporates four key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. Strength of evidence was graded based on our level of confidence that the evidence reflects the true effect of the intervention on the outcome (i.e., how likely further research is to change our confidence in the estimate of effect). Possible grades were “high,” “moderate,” “low,” and “insufficient” (evidence is unavailable or does not permit estimation of an effect).

We graded the strength of evidence for mental health outcomes (KQ 1), chronic medical condition outcomes (KQ 2), and harms (KQ 3). Two reviewers assessed each domain for each key outcome, and differences were resolved by consensus.

Applicability

We assessed applicability of the evidence following guidance from the *Methods Guide for Comparative Effectiveness Reviews*.⁵¹ We used the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence included the following: ethnicity of enrolled populations, type of practice setting, and the use of interventions that may be difficult to incorporate into routine practice for many providers (e.g., they require substantial resources or time, or they may be delivered by research staff rather than existing staff in the practice).

Results

Results are organized by KQ and grouped by medical condition(s) when possible. Our results pertain to the general adult population; no studies that met our inclusion criteria reported on young adults or pregnant women. Regarding older adults, one study selectively recruited for age 60 or older;⁵²⁻⁵⁶ however, participants across all studies in this review tended to be middle aged or older (mean age, 59; range of means, 47 to 72), so we do not report results for older adults separately. Several studies reported on traditionally underrepresented populations, including women,⁵⁷⁻⁵⁹ Spanish speakers,⁵⁷⁻⁶⁰ and predominantly African-American male veterans with HIV;⁶¹ we report these results in the context of overall results by medical condition, not in separate categories.

Results of Literature Searches

We ultimately included 19 published articles reporting on 10 randomized controlled trials. We recorded the reason that each excluded full-text publication did not satisfy the eligibility criteria and compiled a comprehensive list of such studies (Appendix B). Evidence tables for included studies can be found in Appendix C.

Description of Included Studies

In the 10 included trials, sample sizes ranged from 55 to 1,001, and study duration ranged from 6 to 24 months. Nine trials were conducted in the United States (one of these in Puerto Rico) and one in Scotland. All included studies characterized their respective intervention as a form of *collaborative care*, not another form of a practice-based intervention (such as integrated care). Similarly, all included studies specified *depression* as the targeted mental health condition;

no studies specified anxiety as the condition of interest. Accordingly, we use the term depression, instead of mental health condition, when describing the results. The designated chronic medical conditions included arthritis,^{53, 56} cancer,^{52, 57, 59, 62} diabetes,^{37, 39, 58, 63-66} heart disease,⁶⁷ and HIV.⁶¹ Two studies selected patients with one or more active medical conditions.^{60, 68}

All KQs draw from the same universe of evidence. Table ES-2 summarizes key elements of the trial interventions and shows their quality ratings.

Table ES-2. Summary of collaborative care intervention trials

Author/ Trial Name Disease	Quality Rating	Intervention Summary	Delivery Method
			Delivered By Psychiatrist Supervision?
Lin et al., 2003; ⁵⁶ Lin et al., 2006; ⁵³ Fann et al., 2009; ⁵² Williams et al., 2004; ⁵⁵ Katon et al., 2006 ⁵⁴ IMPACT Arthritis, cancer, diabetes	Fair	Care management based on stepped care treatment algorithm; patient preference for treatment: antidepressants or problem-solving therapy (6–8 sessions); monitoring of treatment response	In-person and telephone Depression care specialist (nurse or clinical psychologist) Yes
Dwight-Johnson et al., 2005 ⁵⁷ MODP Cancer	Fair	Described as being based on the IMPACT model	In-person and telephone Bilingual cancer depression care specialist (master's level social worker) Yes
Ell et al., 2008 ⁵⁹ ADAPT-C Cancer	Fair	Described as being based on the IMPACT model	In-person and telephone Bilingual cancer depression care specialist (master's level social worker) Yes
Ell et al., 2010 ⁵⁸ MDDP Diabetes	Fair	Described as being based on the IMPACT model	In-person and telephone Bilingual diabetes depression care specialist (master's level social worker) Yes
Ciechanowski et al., 2006; ³⁹ Katon et al., 2008; ⁶³ Katon et al., 2004; ³⁷ Kinder et al., 2006; ⁶⁴ Lin et al., 2006; ⁶⁵ Simon et al., 2007 ⁶⁶ Pathways Diabetes	Fair	Described as being based on the IMPACT model	In-person and telephone Depression clinical specialist (nurse) Yes

Table ES-2. Summary of collaborative care intervention trials (continued)

Author/ Trial Name Disease	Quality Rating	Intervention Summary	Delivery Method
			Delivered By Psychiatrist Supervision?
Katon et al., 2010 ⁶⁸ TEAMcare Diabetes +/- heart disease	Fair	Support for self-care of depression (including pharmacotherapy) and individualized goal-setting; treat-to-target program for DM and/or CHD; motivational coaching; maintenance support	In-person and telephone Medically supervised nurse trained in diabetes education Yes
Pyne et al., 2011 ⁶¹ HITIDES HIV	Good	Stepped care approach; education/activation; recommendations for medications and/or mental specialty referral; web-based decision support	Telephone Off-site depression care team: nurse depression care manager, pharmacist, psychiatrist Yes
Rollman et al., 2009 ⁶⁷ Bypassing the Blues Heart disease	Good	Education on depression and CHD; support to PCP on antidepressants; referral to mental health specialists as needed; phone monitoring for symptoms	Telephone Nurse care manager Yes
Strong et al., 2008 ^{62 a} SMaRT Oncology 1 Cancer	Fair	Manual-based Depression Care for People with Cancer; up to 10 sessions of problem-solving treatment to address coping; progress monitored by telephone; advice on choice of antidepressant if requested	In-person and telephone Nurses with no psychiatry experience Yes
Vera et al., 2010 ⁶⁰ NA ≥1 of the following: diabetes, hypothyroidism, asthma, hypertension, chronic bronchitis, arthritis, heart disease, high cholesterol, stroke	Good	Depression education; antidepressant medications and/or 13 sessions of cognitive behavioral therapy	In-person and telephone Master's level counselor or psychologist Yes

^aStudy took place in the United Kingdom where both primary care and mental health specialty services are free at the point of delivery.

Abbreviations: ADAPt-C, Alleviating Depression Among Patients with Cancer; CHD, coronary heart disease; DM, diabetes mellitus; IMPACT, Improving Mood—Promoting Access to Collaborative Treatment; MDDP, Multifaceted Diabetes and Depression Program; PCP, primary care provider.

For IMPACT,⁵²⁻⁵⁶ Bypassing the Blues,⁶⁷ Symptom Management Research Trials (SMaRT) Oncology 1,⁶² HITIDES (HIV Implementation of Translating Initiatives for Depression into Effective Solutions),⁶¹ the Multifaceted Oncology Depression Program,⁵⁷ and Vera et al.,⁶⁰ the control condition was usual care, which consisted of informing patients of their depression status and advising them to share this information with their primary care provider (PCP). By contrast, Alleviating Depression Among Patients with Cancer (ADAPt-C),⁵⁹ Pathways,^{37, 39, 63, 64, 66} TEAMcare,⁶⁸ and the Multifaceted Diabetes and Depression Program⁵⁸ compared collaborative care with enhanced usual care, which extended usual care by including some degree of additional communication between the research staff or diabetes care manager and the patient's PCP and/or family about the patient's depression status.

Key Findings and Strength of Evidence

Key Question 1a: Intermediate Mental Health Outcomes and Satisfaction With Care

We summarize findings and strength of evidence (SOE) for this question in Table ES-3. Evidence from eight randomized controlled trials and two subgroup analyses indicated that patients receiving a collaborative care intervention had greater improvement in depressive symptoms and in depression treatment response (≥ 50 percent reduction in symptoms) than those receiving usual care (moderate SOE). These results were consistent across medical conditions and reflect clinically meaningful changes on well-accepted measures of depression. The evidence showed that five patients would need to be treated to achieve one more depression response than would be seen with usual care at 6 months, with a number needed to treat [NNT] of six patients at 12 months.

Table ES-3. Summary of results for collaborative care interventions compared with controls for people with depression and one or more chronic medical conditions: intermediate mental health outcomes

Outcome	Summary of Results	Strength of Evidence
Symptom improvement	Greater symptom improvement scores in intervention groups at both 6 months (SMD, 0.45; 95% CI, 0.29 to 0.61) and 12 months (SMD, 0.47; 95% CI, 0.29 to 0.65) compared with control groups (10 studies).	Moderate
Depression-free days	More depression-free days at 12 months for those in intervention groups than usual care groups (4 studies, range of differences between intervention and control groups: 17 to 54 days)	Moderate
Response ($\geq 50\%$ reduction)	Higher rates of depression response in intervention groups than usual care, based on 8 RCTs and 2 RCT subgroup analyses (NNT, 5 at 6 months; NNT, 6 at 12 months)	Moderate
Remission	Remission of depression favored intervention over usual care at 6 months and at 12 months based on 3 RCTs and 2 RCT subgroup analyses (NNT, 8 at 6 months; NNT, 12.5 at 12 months)	Moderate
Recurrence	No studies addressed recurrence of depression	Insufficient
Treatment adherence	Mixed results: 1 trial reported significantly greater adherence to antidepressants in the intervention arm at 6 and 12 months; the other reported no difference between groups at 6 and 12 months.	Insufficient
Treatment satisfaction	Greater satisfaction with care for intervention participants than controls RD, 0.21 (95% CI, 0.11 to 0.30) ^a	Moderate

^a Results are from meta-analysis of the 4 trials that reported satisfaction for both intervention and control arms. Two additional trials reported treatment satisfaction for the intervention arm but not the usual care arm.

Abbreviations: CI, confidence interval; NA, not applicable; NNT, number needed to treat; RCT, randomized controlled trial; RD, risk difference; SMD, standardized mean difference; WMD, weighted mean difference

Although less frequently measured, patients receiving collaborative care also had more depression-free days (moderate SOE) and higher rates of depression remission (moderate SOE) compared with patients receiving usual care. Intervention patients similarly reported greater satisfaction with care (moderate SOE).

Evidence was insufficient (based on limited data) to draw conclusions about adherence to antidepressants (conflicting evidence) or about recurrence of depression (no trial).

Key Question 1b: Morbidity, Mortality, Quality of Life, Function, and Utilization

This question looked at other mental health outcomes, including suicide, use of antidepressants, mental health–related quality of life, use of mental health care services, sick days attributable to mental health, and employment stability (Table ES-4). Only one suicide was reported, in the usual care arm of a cancer trial.⁶² Based on data from three studies at 6 months and five studies at 12 months, use of antidepressants was greater in collaborative care arms than in control groups across populations with various chronic medical conditions (moderate SOE). Quality of life was measured in several ways but most frequently using the mental component of the Medical Outcomes Study Short-Form (SF-12); the trials showed that collaborative care interventions achieved greater quality of life scores than usual care at 6 and 12 months (moderate SOE). Four studies reported on health care utilization; each showed greater use of any mental health services at 6 or 12 months (or both) by those receiving the collaborative care intervention (low SOE). No data were available on sick days or employment stability (insufficient).

Table ES-4. Summary of results for collaborative care interventions compared with controls for people with depression and one or more chronic medical conditions: other mental health outcomes

Outcome	Summary of Results	Strength of Evidence
Suicide	One study reported one suicide in the usual care group	Insufficient
Use of anti-depressants	Greater antidepressant use for collaborative care interventions than for usual care at 6 and 12 months (RD, 0.22; 95% CI, 0.13 to 0.32 at 12 months ^a)	Low
MH-related quality of life	Greater mental health–related quality of life for subjects in collaborative care intervention arms than usual care at 6 and 12 months using the mental component of the Medical Outcomes Study Short Form (WMD, 2.98; 95% CI, 1.41 to 4.56 at 12 months)	Moderate
MH care utilization	Greater use of any mental health services for collaborative care interventions than for usual care at 6 and/or 12 months (42% to 97% vs. 16% to 57% for intervention and control groups, respectively; based on 4 studies)	Low
MH-related sick days	Not reported	Insufficient
MH-related employment stability	Not reported	Insufficient

^a Results of the meta-analysis excluding the HITIDES data

Abbreviations: CI, confidence interval; HITIDES, HIV Implementation of Translating Initiatives for Depression into Effective Solutions; MH, mental health; RD, risk difference; WMD, weighted mean difference.

Key Question 2a: Intermediate Chronic Medical Outcomes

For this question, we were interested in the effects of collaborative care interventions on intermediate outcomes for the specified chronic medical condition(s). For most chronic medical conditions of interest here, we found just one study (Table ES-5). We found multiple studies of people with diabetes and depression.

Table ES-5. Summary of results for collaborative care interventions compared with controls for people with depression and one or more chronic medical conditions: intermediate chronic medical outcomes

General Outcome	Specific Disease-Related Outcome	Summary of Results	Strength of Evidence
Symptom improvement	Arthritis: pain	Insufficient evidence from 1 subgroup analysis to draw conclusions.	Insufficient
	HIV: symptom severity	Insufficient evidence from 1 RCT to draw conclusions.	Insufficient
• Response	Diabetes: HbA1c	3 RCTS and 1 subgroup analysis showed no between-group differences at 6 or 12 months.	Low
	Heart disease: ≥ 10 mmHg decrease in SBP	Insufficient evidence from 1 RCT to draw conclusions.	Insufficient
• Adherence	Cancer: followed treatment	Insufficient evidence from 1 RCT to draw conclusions.	Insufficient
	Diabetes: diet	Not calculated; no between-group difference at any time points in all studies examined.	Moderate
	Diabetes: exercise	2 trials favored intervention; 1 trial found no difference.	Low
	Diabetes: medications	Insufficient evidence from 2 studies (1 RCT, and 1 subgroup analysis) to draw conclusions.	Insufficient
	HIV: medications	Insufficient evidence from 1 RCT to draw conclusions.	Insufficient
• Satisfaction with care	Diabetes, heart disease, or both	Insufficient evidence from 1 RCT to draw conclusions.	Insufficient

Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c; mmHg, millimeters of mercury; OR, odds ratio; RCT, randomized controlled trial; SBP, systolic blood pressure; WMD, weighted mean difference.

HbA1c was reported as a measure of response in four trials of people with diabetes; baseline HbA1c ranged from 7.28 percent to 9.03 percent. Our meta-analyses found no significant differences between intervention and control groups (WMD, 0.13; 95% CI -0.55 to 0.41 at 6 months; WMD, 0.24; 95% CI, -0.14 to 0.62 at 12 months) (low SOE). However, the only study to use HbA1c as a predefined outcome measure, the TEAMcare study,⁶⁸ reported significant differences in HbA1c. The figures were as follows for intervention versus control groups: 8.14 versus 8.04 at baseline; 7.42 versus 7.87 at 6 months; and 7.33 versus 7.81 at 12 months (overall $p < 0.001$).

Three studies reported on adherence to recommended treatment.^{55, 65, 68} The subjects in the collaborative care intervention were no more likely than controls to adhere to a generally healthy diet (low SOE), but they were more likely to adhere to an exercise program in two of three studies (low SOE). For rates of adherence to an overall regimen (including oral hypoglycemics, lipid-lowering agents, and angiotensin-converting enzyme inhibitors), evidence was insufficient to draw conclusions.

Data were insufficient to draw conclusions about treatment satisfaction.

Key Question 2b: General Health Outcomes and Costs

General health outcomes of interest included condition-specific morbidity, mortality, health care utilization, and quality of life. All evidence was insufficient to draw conclusions other than for mortality and quality of life (Table ES-6).

Table ES-6. Strength of evidence for collaborative care interventions for people with depression and one or more chronic medical conditions: KQ 2b, general health outcomes and costs

Outcome	Summary of Results	Strength of Evidence
Condition-specific morbidity	Insufficient evidence from 1 RCT (post-CABG) and 1 subgroup analysis (arthritis) to draw conclusions.	Insufficient
Mortality	Eight studies reported no difference between groups, with few overall events; 6 months: RD, 0.00 (95% CI, -0.02 to 0.02); 12 months: RD, 0.00 (95% CI, 0.02 to 0.01).	Moderate
Health care utilization	Data were insufficient to draw conclusions about use of health care services.	Insufficient
Quality of life	Greater quality of life for those receiving collaborative care at 6 and 12 months, based on several different measures.	Moderate
Cost of intervention	Data were insufficient because of no comparator data; intervention costs were reported for the intervention arm in 6 studies, using varying methods.	Insufficient

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; RCT, randomized controlled trial; RD, risk difference

Eight studies reported on mortality and few deaths were reported overall. Most occurred in studies of people with cancer. Intervention and control subjects did not differ in mortality at 6 months (risk difference [RD], 0.00; 95% CI, -0.02 to 0.02) or 12 months (RD, 0.00; 95% CI, -0.02 to 0.01) (moderate SOE). Patients receiving collaborative care interventions generally experienced greater quality of life than control patients at 6 and 12 months, based on several different measures from six studies (moderate SOE).

Key Question 3: Harms

Very little data were reported on harms, leaving insufficient evidence to draw conclusions. Only the TEAMcare study, in patients with depression, diabetes, and/or heart disease,⁶⁸ defined adverse events; the investigators reported higher rates of mild adverse events (e.g., medication side effects) and of moderate adverse events (e.g., falls) in the intervention arm. These could be attributable more to increased rates of medication adjustment than to the overall collaborative care intervention itself. Additionally, patients in the intervention arm had more frequent contacts with the care manager and thus had more opportunities to report adverse events, so findings might be the result of detection bias.

Key Question 4: Characteristics of Service Interventions

All interventions were described as collaborative care interventions; we found no study with any other types of practice-based interventions that met our inclusion/exclusion criteria.

The summary finding was that collaborative care hinged on the role of care manager, whose training and expertise varied widely. A physician (9 of 10 were psychiatrists) supervised care; a form of stepped care, patient preferences for treatment, and self-management were central to most interventions.

The TEAMcare study was the most original in its design. Its investigators had a goal not just of reducing depression, but also controlling risk factors for various diseases simultaneously using a nurse to support guideline-concordant care.

Key Question 5: Characteristics of the Practice Setting

Given that characteristics of the practice setting often determine the feasibility of implementing interventions, we were interested in assessing similarities and differences. Nine of

10 trials were conducted in the United States (1 in Puerto Rico). Overall, practice setting characteristics (e.g., location, practice type and size, open/closed system, level of integration, payer mix and payer type, service mix, information technology) and system characteristics (e.g., financing of care and payment arrangements) were rarely reported. We categorized the system as open (no membership or eligibility required) in six trials^{57-60, 62, 67} and closed in three trials.^{37, 39, 61, 63-66, 68} Closed systems were generally self-contained; in this evidence base, they included Group Health Cooperative and the Department of Veterans Affairs (VA) system, where an array of services was accessible to patients who were members of these organizations. This latter factor may be important for applicability because of the nature of collaborative care and its focus on coordination, which is arguably easier in a closed than an open system of care.

Discussion

In primary care patients with depression and one or more specific chronic medical conditions, collaborative care interventions achieved improvement in depression symptoms, response, remission, and depression-free days (moderate SOE); satisfaction with care (moderate SOE); and mental and physical quality of life (moderate SOE). These improvements were consistent across different common chronic medical conditions. Patients with diabetes receiving collaborative care had greater adherence to some aspects of self-care (low SOE) but no difference in HbA1c (low SOE).

Our findings reinforce the evidence for the effectiveness of collaborative care interventions for treating depression in primary care.³⁵ Moreover, they add a level of detail that previously (to our knowledge) had not been systematically reviewed. We selected trials that required the diagnosis of one or more chronic diseases (rather than generic primary care samples), and we reported on both the depression and the medical outcomes. This review also extended the parameters of primary care to include settings in which certain patients with chronic disease receive the majority of their care. We found that recipients of collaborative care had significantly greater improvement in depression outcomes than patients receiving usual care, for people with arthritis, cancer, diabetes, heart disease, and HIV.

Although the relationship between depression and chronic disease is established,^{28, 69, 70} to what extent successful treatment of depression improves chronic medical conditions remains uncertain. Our review shows that investigators are beginning to examine these outcomes, particularly in diabetes, although largely as secondary outcomes and with inconclusive data at present.

One study in the review, TEAMcare,⁶⁸ is an exception because it identified markers of disease risk for multiple conditions as primary outcomes. Using a guideline-based “treat-to-target” approach delivered by a medically trained nurse, these investigators targeted patients with poorly controlled diabetes, coronary artery disease, or both and coexisting depression; their aim was to reduce overall risk factors. This approach is a detour from the traditional model, where the focus is on collaborative care of depression, presumably in the hope that treating depression will improve overall health. Perhaps partly because of the benefits of having an integrated health care system, TEAMcare recipients showed clear improvements not only in depression, but also in reducing HbA1c and SBP to target goals.

Applicability

Our findings are generally applicable to primary care patients with depression (we found no studies of anxiety) and at least one chronic medical condition, but they may not apply to patients

with medical conditions not addressed in this report. People of Hispanic origin (predominantly female)⁵⁷⁻⁵⁹ and male veterans⁶¹ were represented and appeared to respond similarly across outcomes, but there were too few data to analyze separately. Reported studies used clinically meaningful measures and had study durations (at least 6 months) that provided a real-world context.

Although these trials represented several different settings, including primary care–like cancer and HIV clinics, they all had in common a care manager who directed the intervention. The intermediate mental health outcomes achieved might, therefore, apply only to settings that can accommodate and afford to provide such services. Similarly, practices that agreed to participate in these trials may reflect a selection bias based on existing culture and willingness to collaborate.

Research Gaps

Depression Treatment and Outcomes of Chronic Disease

Depression can negatively affect general medical illness, but it is less well known whether the effective treatment of depression in the primary care setting can alter the course of chronic disease. To determine the relative benefit of implementing such programs, more studies are needed that are designed to measure the effect of depression care on medical outcomes in depressed primary care patients with medical conditions.

A growing body of literature is emerging for diabetes and heart disease (although still few focus on medical outcomes). Other common conditions, such as chronic lung disease and pain syndromes, need investigation. Researchers should try to recruit selectively patients with common disease clusters, such as diabetes, hypertension, and obesity concomitant with depression; this group may be particularly salient given the probable role of vascular disease in late-onset depression.^{71, 72}

More generally, the bidirectional aspect of depression and medical illness needs further exploration. For example, investigators could usefully study whether improving vascular risk factors reduces depression.

Anxiety

We found no eligible studies involving anxiety. Given the significant medical morbidity and health care utilization associated with anxiety in primary care,⁷³ this absence is striking. Practice-based models of care targeted to this population should be tested. One reason for the lack of research to date on such patients may be that the steps of screening and diagnosis of anxiety disorders in the primary care setting are less mature than they are for depression. Nonetheless, the feasibility of this work has been shown.³⁶

Head-to-Head Trials

Head-to-head trials of practice-based interventions should be considered; these might include collaborative care versus mental health co-location or another model of integrated care versus collaborative care. Given the desire to find the active ingredients of practice-based care,⁴⁰ investigators should test variations of existing efficacious models. Certain components of the collaborative care model may be more salient than others, and future studies that explicitly compare intervention components within the collaborative care model may help address this issue. For example, head-to-head comparisons of telephone-based versus face-to-face approaches

might be useful. Examining session frequency and/or study intensity (i.e., frequency plus duration) as a predictor of outcome within these two approaches may also prove fruitful.

Exploring the extent to which mental health and physical health outcomes are related to the intervention provider's training is another important issue; that could entail determining whether, for instance, outcomes improve by having a depression care specialist deliver the intervention rather than a provider not trained in mental health.

Answering some of these basic design questions in ways that facilitate comparisons with true interventions, and not simply usual care, will ultimately facilitate translation and implementation of these approaches on a broader scale.

Conclusions

Collaborative care interventions improved outcomes for depression and quality of life in primary care patients with multiple different medical conditions. Future studies should target a broader range of specific medical conditions, or clusters of conditions, and should compare variations of practice-based interventions to examine determinants of effectiveness.

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Introduction

Background

The World Health Organization has identified the integration of mental health into primary care as the most salient means of addressing the burden of mental health conditions, noting its “urgent importance.”¹ In the United States, half of the care for common mental health disorders is delivered in general medical settings,² emphasizing the vital role that primary care providers play in the diagnosis and treatment of these disorders.

Common mental health conditions, such as depression and anxiety, are found in up to 10 percent of primary care patients,³ and these conditions often coexist with chronic medical conditions. Accordingly, considerable interest has been expressed in improving the recognition and management of mental health conditions, especially depression, within primary care.⁴⁻⁶ Specifically, interest is emerging about whether treatment of common mental health conditions in primary care can improve both mental health and chronic medical outcomes. The arena of mental health and primary care is moving from consideration of single conditions and their outcomes to more real-world, complex-care paradigms.^{2,7} However, to date, no synthesis of the evidence has been done in a way that accounts for the primary care patient with “multiple chronic conditions”⁸ and examines both mental health and chronic medical outcomes simultaneously.

Mental Health Conditions

According to the National Comorbidity Survey Replication, 12-month prevalence of any mental health disorder in the United States is 26.2 percent; more than half of these cases (14.4 percent) meet criteria for only one disorder, and smaller proportions meet criteria for two (5.9 percent) or more disorders (5.9 percent).⁹ Anxiety disorders are by far the most prevalent class of disorders (18.1 percent), followed by mood disorders (9.5 percent); anxiety and mood disorders often co-occur.⁹

The overall prevalence of mental health disorders appears to be equal in men and women. However, women have a higher prevalence of depression and most anxiety disorders.¹ The groups most likely to have unmet mental health care needs include the elderly, children and adolescents, members of ethnic minorities, the uninsured, low-income individuals, and individuals who complain predominantly of physical symptoms as a manifestation of their mental health problem.²

Of the mental health conditions, depression and anxiety cause the greatest societal burden as measured by social and economic costs.¹⁰ Indeed, by 2030, depression itself is projected to be the single leading cause of overall disease burden in high-income countries.¹¹ Worldwide, depression makes a large contribution to the burden of disease, ranking third worldwide, eighth in low-income countries, and first in middle- and high-income countries.¹² In 2000, the U.S. economic burden of depressive disorders was estimated to be \$83.1 billion.¹³ More than 30 percent of these costs are attributable to direct medical expenses.¹³ The economic burden of anxiety disorders is similarly high, with cost estimates reaching \$54.9 billion per year.¹⁴

Chronic Medical Conditions

Half of all Americans live with a chronic medical condition.¹⁵ An estimated 23.6 million people (7.8 percent of the U.S. population) have diabetes.¹⁶ Roughly 24 million U.S. adults have chronic obstructive pulmonary disease, and an additional 23 million have asthma.¹⁷ Up to one-quarter of people living with chronic medical conditions have limitations in daily activity.¹⁵

Chronic medical conditions are significant drivers of health care costs. In a study conducted in 2001 and 2002,¹⁸ an estimated 13 percent of the total U.S. workforce experienced a loss in productive time during a 2-week period because of pain (including arthritis), costing an estimated \$61.2 billion per year. In 2010, cardiovascular, lung, and blood diseases were projected to cost \$486 billion in health care expenditures, not including lost productivity or costs attributed to them as secondary causes of morbidity and mortality.¹⁷ Living with chronic disease also takes a personal and emotional toll on patients and their family members, owing to significant reductions in quality of life.¹⁵

Concomitant Mental Health and Chronic Medical Conditions

Chronic medical conditions commonly associated with depression (Table 1) and/or anxiety include arthritis, heart disease, diabetes, asthma, lung disease, and cancer.^{19, 20} Comorbid depression among people with chronic physical illness has been linked to an increase in health care utilization, disability, and work absenteeism when compared with those without comorbid depression, even after controlling for the varying burden of the physical health condition.²¹ In one study of primary care outpatients with hypertension, diabetes, and/or heart disease, between 26 percent and 28 percent of patients reported a diagnosis of anxiety disorder at some point in their lives.²²

Table 1. Prevalence of depression in chronic medical conditions

Chronic Condition	Prevalence of Depression
Arthritis	
Rheumatoid arthritis	13%-20% ^{23, 24}
Osteoarthritis	19.4% ²⁵
Heart disease	
Post-myocardial infarction	10%-47% ²⁶
Coronary artery disease	15% ²⁷ -23% ²⁸
Diabetes	11%-15% ²⁹ (MDD specifically) 17.6% ³⁰ -31.0% ²⁹ (any depressive disorder)
Pulmonary disease	
Asthma	26.6% ³¹
Chronic obstructive pulmonary disease	27.2% ³²
Cancer	9%-24% ³³ (MDD) 20%-50% ³³ (any depressive disorder)

Abbreviations: MDD, major depressive disorder

Treating Mental Health Conditions in Primary Care

Strategies addressing the management of mental health conditions in primary care have focused on depression. Repeated evidence reviews show the benefits of integrated and collaborative care models, as compared with usual care, on the outcomes of depression in the general health setting.^{4, 34, 35} Literature on the treatment of other mental health conditions such as anxiety in primary care is less mature, but data suggest that such conditions may also be successfully treated in primary care.³⁶ Further, an emerging literature addresses whether better treatment of depression in primary care can also improve chronic medical outcomes, such as for

diabetes.³⁷⁻³⁹ A review of similar studies will help address the clinical uncertainty about whether such collaborative interventions can make a difference in more than one disease outcome and inform policy decisions about the potential benefit of adopting such guidance.

Scope and Key Questions

Previous Reports

Two recent reports have particular relevance to this topic: a 2008 Agency for Healthcare Research and Quality (AHRQ) report examining the integration of mental health/substance abuse and primary care³⁴ and a 2009 National Institute for Health and Clinical Excellence (NICE) guideline for depression in adults with a chronic physical health problem.³⁵ These reports neither specified primary care as the setting of interest nor examined disease-specific chronic medical outcomes; this review addresses both.

Scope of the Review

This review summarizes the body of evidence that examines the effectiveness of practice-based interventions targeting primary care patients with both depression or anxiety and a chronic medical condition(s). Narrowing the scope in this way selects for a population with known burden and associated higher risk for poor outcomes, and doing so can help answer the uncertainty about whether such focused efforts can improve more than one condition at a time. In an effort to address the inherent heterogeneity of complex interventions,⁴⁰ this report also compares the specific characteristics of the interventions and the practice settings in which they are delivered.

These results should be of interest to multiple stakeholders, including patients, providers, and policymakers. A family physician nominated this topic because he wanted to know whether concomitantly treating mental health and general health conditions in the primary care setting could improve overall health outcomes and prevent the fragmentation of services across providers. As we move to consider shared savings programs, such as accountable care organizations,⁴¹ and the patient-centered medical home,⁴¹ consumers and payers are eager to identify interventions and processes that can streamline care for multiple conditions and improve the quality and efficiency of care. Interestingly, numerous barriers—many financial—hinder implementation of collaborative depression treatment in primary care despite its considerable evidence base.^{4, 42, 43} This report aims to provide new data about the common and costly problem of primary care patients with concomitant mental health and chronic medical conditions. Such information can inform clinical decisionmaking as well as potential reimbursement and coverage strategies.

As we conceptualized the approach to this report, preliminary evidence reviews revealed that data were insufficient on mental health conditions other than depression and anxiety that met our eligibility criteria. To reduce confusion regarding the universe of potential mental health conditions, therefore, the remainder of this report focuses on depression and anxiety.

Population

The main focus of this review is adults with one or more diagnosed chronic medical condition and a diagnosis of either depression or anxiety (or both) who are being treated in a primary care setting. An example is patients with diabetes and depression. The purpose is to include patients not just with symptoms of disease, but also those with a level of severity known

to benefit from treatment and to be associated with poor outcomes. Settings include traditional primary care (e.g., family medicine, internal medicine, obstetrics/gynecology, and geriatrics) and settings with a primary care–type relationship (e.g., oncology clinics for those with cancer, infectious disease clinics for those with HIV).

Interventions

For this review we use the term “practice-based” to define the interventions of interest. This term reflects an explicit effort to be inclusive of a wide range of interventions while also requiring the primary care site to be the nucleus of activity. Our rationale is to honor the spirit of the original nomination by acknowledging the crucial role of primary care, where most patients receive care, and from which care is optimally coordinated.⁴⁴

Practice-based is understood to mean any intervention that (1) targets the *care process* within a system of care and (2) aims to improve the mental health condition or both the mental health and chronic medical conditions. Examples of practice-based interventions include, but are not limited to, coordinated care, integrated care, and collaborative care; they often involve a care manager. Because of the dual focus on (1) concurrent management of both the mental health and the chronic medical condition within primary care and (2) systematic changes that can improve the delivery of care (rather than testing specific interventions), we exclude medication-only, device, and psychotherapy-only clinical trials (e.g., efficacy studies comparing a medication with a placebo) from this review. Practice-based interventions can include person-level components such as problem-solving therapy and antidepressant medications, but they must be delivered as part of a broader systematic strategy to improve care.

Key Questions

- Key Question (KQ) 1a: Among adults with chronic medical conditions and concomitant depression and/or anxiety (such as patients with diabetes and depression) treated in the primary care setting, what is the comparative effectiveness of practice-based interventions aimed at improving the mental health condition or both the mental health and chronic medical conditions (when compared with similar interventions or usual care) on intermediate depression/anxiety outcomes (e.g., symptom improvement)?
- KQ 1b: Among adults with chronic medical conditions and concomitant depression and/or anxiety (such as patients with diabetes and depression) treated in the primary care setting, what is the comparative effectiveness of practice-based interventions aimed at improving the mental health condition or both the mental health and chronic medical conditions (when compared with similar interventions or usual care) on other mental health outcomes (e.g., depression-related quality of life) and mental health–related utilization?
- KQ 2a: Among adults with chronic medical conditions and concomitant depression and/or anxiety (such as patients with diabetes and depression) treated in the primary care setting, what is the comparative effectiveness of practice-based interventions aimed at improving the mental health condition or both the mental health and chronic medical conditions (when compared with similar interventions or usual care) on intermediate chronic medical outcomes (e.g., hemoglobin [Hb]A_{1c} for patients with diabetes)?
- KQ 2b: Among adults with chronic medical conditions and concomitant depression and/or anxiety (such as patients with diabetes and depression) treated in the primary care setting, what is the comparative effectiveness of practice-based interventions aimed at

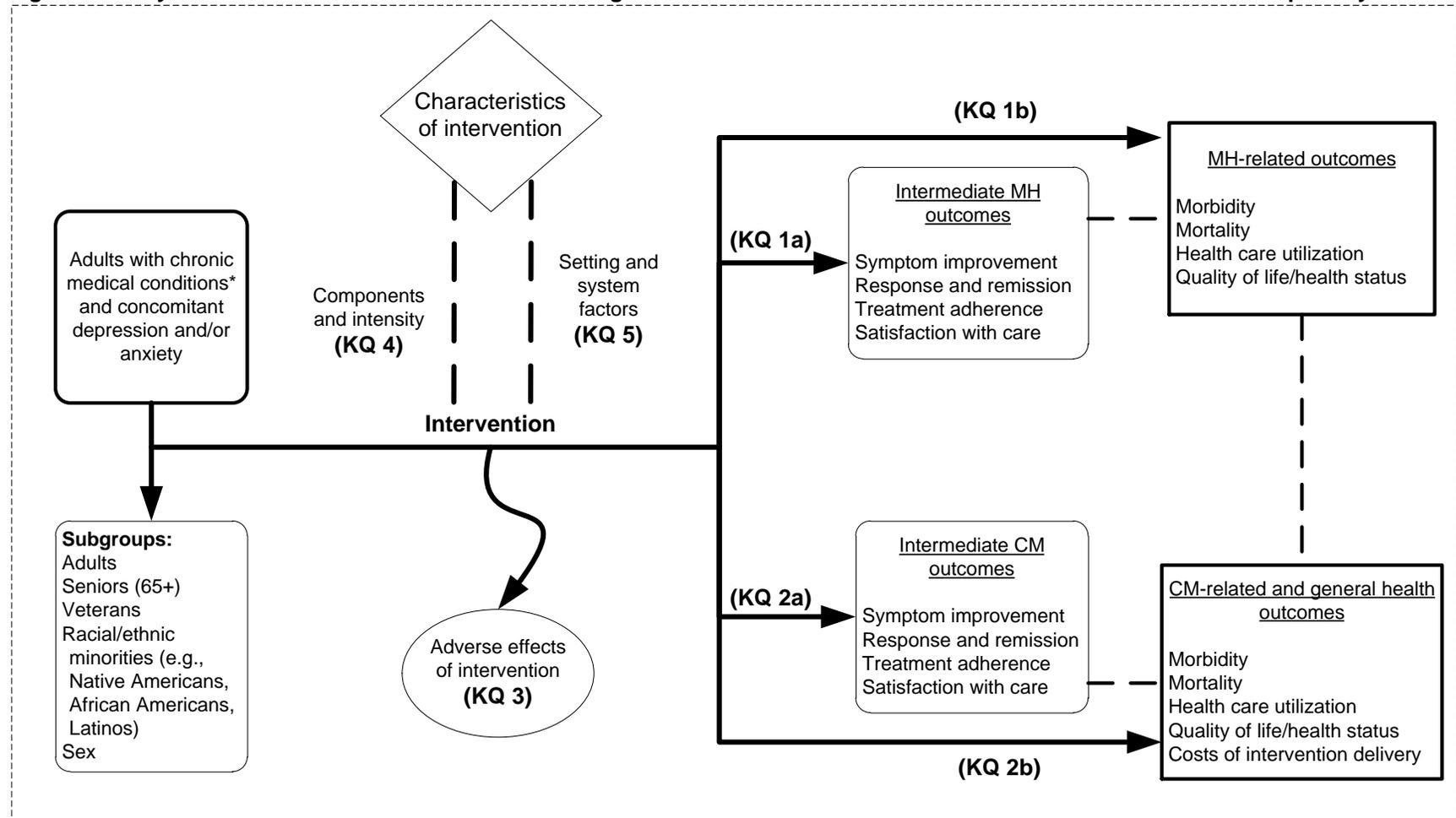
improving the mental health or both the mental health and chronic medical conditions (when compared with similar interventions or usual care) on general health outcomes (e.g., diabetes-related morbidity)?

- KQ 3: What harms are associated with practice-based interventions for primary care patients with chronic medical conditions and concomitant depression and/or anxiety?
- KQ 4: What are the characteristics of the practice-based interventions addressing concomitant mental health and chronic medical conditions used in the primary care setting with regard to specific components and/or intensity (e.g., visit frequency, total number of contacts, provider discipline, use of self-management)?
- KQ 5: What are the specific characteristics of the practice setting where the interventions were delivered with regard to such variables as organizational characteristics (e.g., decision support, level of integration, information technology, electronic medical record, presence of mental health services on site, payer and service mix, practice size, and practice location/setting) or the relationship between elements of the system in which the practice operates (e.g., coordination, financing of care, payment arrangements).

Analytic Framework

We developed an analytic framework to guide the systematic review process (Figure 1). KQ 1 addresses the effectiveness of practice-based interventions for improving mental health outcomes—1a addresses intermediate clinical outcomes related to mental health, such as symptom response, and 1b addresses other outcomes related to mental health, such as depression-related quality of life, and mental health care utilization. KQ 2 addresses the effectiveness of practice-based interventions for improving chronic medical condition outcomes—KQ 2a addresses intermediate clinical outcomes, such as pain severity scores for patients with chronic pain, and 2b addresses other important chronic medical outcomes, such as disease-related quality of life, and general health-related utilization. KQ 3 addresses the potential harms of practice-based interventions. KQs 4 and 5 assess the characteristics of the interventions and practice settings, respectively.

Figure 1. Analytic framework for interventions addressing concomitant mental health and chronic medical conditions in primary care



* Chronic medical conditions are considered broadly and include the AHRQ priority conditions and IOM priority conditions, including diabetes, arthritis, and chronic pain, among others.

Abbreviations: CM, chronic medical; MH, mental health.

Methods

The methods for this comparative effectiveness review (CER) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>). The main sections in this chapter reflect the elements of the protocol established for this CER; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.⁴⁵

Topic Refinement and Review Protocol

During the topic development and refinement processes, we generated an analytic framework, preliminary Key Questions (KQs), and preliminary inclusion/exclusion criteria in the form of PICOTS (Population, Intervention, Comparison, Outcome, Timing, Setting), and study design. The processes were guided by the information provided by the topic nominator, a scan of the literature, methods and content experts, and Key Informants. We worked with five Key Informants during the topic refinement, and seven additional individuals participated in the Technical Expert Panel (TEP). Key Informants and TEP members participated in conference calls and discussions through email to review the analytic framework, KQs, and PICOTS at the beginning of the project; TEP members also discussed the preliminary assessment of the literature, including inclusion/exclusion criteria and review of the protocol, and provided input on the information and categories included in evidence tables.

To achieve an appropriate scope for the review, we prioritized conditions and interventions that were most clinically relevant. With input from our Key Informants, we selected the two mental health conditions most commonly encountered by primary care providers (depression and anxiety) and the following chronic medical conditions identified as priority conditions by AHRQ⁴⁶ and the Institute of Medicine:⁴⁷ arthritis; diabetes; asthma or chronic obstructive pulmonary disease (COPD); cancer; chronic pain; stroke; HIV/AIDS; heart disease, heart failure, myocardial ischemia, coronary artery bypass graft, post-myocardial infarction, and coronary artery disease; “complex” patients with multiple comorbidities; and frailty due to old age.

Our KQs were posted for public comment on AHRQ’s Effective Health Care Web site from March 18, 2011, through April 15, 2011; we put them into final form after review of the comments and discussion with the TEP.

Literature Search Strategy

Search Strategy

To identify articles relevant to each KQ, we searched MEDLINE[®], Embase, the Cochrane Library, CINAHL[®], and PsycINFO[®]. The full search strategy is presented in Appendix A. We used Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate, focusing on terms to describe the relevant population and the interventions of interest. We reviewed our search strategy with the TEP members and incorporated their input into our search strategy.

We limited the electronic searches to English language (because of time and other resources) and humans. Sources were searched from the inception of each database through May 23, 2011.

We used the National Library of Medicine publication type tags to identify reviews, randomized controlled trials, and meta-analyses.

We manually searched reference lists of pertinent reviews, included trials, and background articles on this topic, including the 2008 AHRQ report on integration of care,³⁴ to look for any relevant citations that might have been missed by our searches. We imported all citations into an electronic database (EndNote® X4). We also searched for unpublished studies relevant to this review using ClinicalTrials.gov and the World Health Organization’s International Clinical Trials Registry Platform.

We will also conduct an updated literature search (of the same databases searched initially) concurrent with the peer review process. Any literature suggested by Peer Reviewers or from the public will be investigated and, if appropriate, incorporated into the final review. Appropriateness will be determined by the same methods listed above.

Inclusion and Exclusion Criteria

We developed eligibility (inclusion and exclusion) criteria with respect to patient PICOTS, and study designs and durations for each KQ (Table 2). Appendix B contains the list of studies that were reviewed at the full-text stage but failed to meet all inclusion criteria.

Table 2. Study eligibility criteria

Criteria	Definition
Population(s)	Adults (age 18 or older) with depression and/or anxiety and one or more of the following chronic medical conditions: arthritis; diabetes; asthma or chronic obstructive pulmonary disease; cancer; chronic pain; stroke; HIV / AIDS; heart disease, heart failure, myocardial ischemia, coronary artery bypass graft, post-myocardial infarction, or coronary artery disease; “complex” patients with multiple comorbidities; and frailty due to old age. Depression and anxiety are defined as threshold-level conditions, meeting criteria for a disorder as determined by valid and reliable measures with established cutpoints to exclude subthreshold symptoms and minor depression.
Interventions	Practice-based interventions aimed at improving the mental health condition or both the mental health and chronic medical conditions. A practice-based intervention is one that targets the <i>care process</i> within a system of care. Examples of practice-based interventions include coordinated care, integrated care, and collaborative care.
Comparators	Different combinations, approaches, and modalities for the above interventions Usual care (as defined by the study, representing, however a particular practice or setting is providing care for patients who do not receive an intervention)
Outcomes	<u>Intermediate mental health outcomes:</u> <ul style="list-style-type: none"> • symptom improvement, response rates, and remission and/or recurrence as measured by scores on reliable and valid instruments (to include self-rated instruments) ; • treatment adherence; and • satisfaction with care. <u>Intermediate chronic medical condition outcomes:</u> <ul style="list-style-type: none"> • symptom improvement, remission, and remediation; • response to treatment (e.g., HbA1c); • treatment adherence; and • satisfaction with care. <u>Other mental health–related outcomes:</u> <ul style="list-style-type: none"> • disease-related mortality, • disease-related morbidity, • disease-related functional status, • mental health–related quality of life, • sick days related to mental health,

Table 2. Study eligibility criteria (continued)

Criteria	Definition
Outcomes (continued)	<p><u>Other mental health–related outcomes (continued):</u></p> <ul style="list-style-type: none"> • mental health care utilization, and • employment stability. <p><u>Other chronic medical and general health outcomes:</u></p> <ul style="list-style-type: none"> • all-cause mortality, • disease-related mortality, • disease-related morbidity, • disease-related functional status, • general health–related quality of life, • disease-specific outcomes, • general health care utilization, • total sick days and sick days due to general health condition, • employment stability, and • costs of intervention delivery. <p><u>Potential adverse effects of interventions:</u></p> <ul style="list-style-type: none"> • adverse effects of pharmacotherapy and • other harms as reported.
Timing	Outcome assessment at least 6 months after randomization (or from receipt of the intervention for nonrandomized controlled trials)
Settings	<p>Traditional primary-care settings; settings with a primary care-type relationship that may be applicable to traditional primary care settings (e.g., infectious disease clinics for people with HIV, oncology clinics for people with cancer).</p> <p>No geographic limits.</p>
Study designs	<p>Randomized controlled trials, nonrandomized trials with concurrent eligible controls, and recent systematic reviews with or without meta-analyses.</p> <p>No sample size limits.</p>

Abbreviations: HbA1c, hemoglobin A1c.

Data Extraction

For studies that met our inclusion criteria, we abstracted important information into evidence tables. We designed and used structured data abstraction forms to gather pertinent information from each article, including characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers extracted the relevant data from each included article into the evidence tables. A second member of the team reviewed all data abstractions against the original article for completeness and accuracy. We recorded intention-to-treat results if available. All data abstraction was performed using Microsoft Excel[®] software. Data abstraction forms were almost identical to the evidence tables containing abstracted data (Appendix C).

Quality Assessment of Individual Studies

To assess the quality (internal validity) of studies, we used predefined criteria based on those developed by the U.S. Preventive Services Task Force (USPSTF) (ratings: good, fair, poor)⁴⁸ and the University of York Centre for Reviews and Dissemination.⁴⁹ In general terms, a “good” study has the least risk of bias and its results are considered to be valid. To be rated “good” for the purpose of this review, a study must have fulfilled all of the following criteria: adequate randomization of patients; adequate allocation concealment; blinded outcome assessors; similar baseline characteristics across treatment arms; overall attrition less than 20 percent; differential

attrition less than 15 percent (i.e., there is less than a 15 percentage point difference between attrition in one group and attrition in another); intention-to-treat analysis; and use of equivalent, valid, and reliable outcome measures. A “fair” study is susceptible to some bias but probably not sufficient to invalidate its results. A “poor” study has significant risk of bias (e.g., stemming from serious errors in design or analysis) that may invalidate its results.

Two independent reviewers assigned quality ratings for each study. Disagreements between the two reviewers were resolved by discussion and consensus or by consulting a third member of the team. We gave poor quality ratings to studies that had a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories, and we excluded them from our analyses. Appendix D details the criteria used for evaluating the quality of all included studies.

Data Synthesis

Overall Approach

The research team determined prioritization and/or categorization of outcomes with input from TEP members. Quantitative analyses were conducted using meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough that combining their results could be justified. To determine whether quantitative analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies under consideration following established guidance.⁵⁰ We did this by qualitatively assessing the PICOTS of the included studies, looking for similarities and differences. When quantitative analyses were not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we synthesized the data qualitatively.

Statistical Analyses

We ran meta-analyses for outcomes with sufficient data, including depression symptom improvement, reduction of depression symptoms, remission of depression, mental health treatment satisfaction, mental health status, prescription antidepressant use, change in hemoglobin A1c (HbA1c), change in physical health status, and all-cause mortality. For continuous outcomes of mean score change between baseline and endpoint, many studies did not report a variance measure of the mean change but did include variance information at baseline and 12 months. In these cases, we assumed a correlation of 0.5 to estimate the mean change variance⁵¹ and conducted sensitivity analyses with assumed correlations of 0.3 and 0.7 to confirm that this assumption did not significantly change our results. However, in cases in which the final mean value was adjusted for baseline via regression or analysis of covariance (ANCOVA), we used this endpoint value instead of assuming a correlation because it is the most efficient and least-biased statistic.⁵² Separate analyses were run for studies reporting 6- and 12-month outcomes.

We used random-effects models to estimate pooled effects.⁵³ For continuous outcomes, the effect measure was the weighted mean difference (WMD) or, if the measurement scale differed among trials, the standardized mean difference was calculated. For most dichotomous outcomes, we report risk differences. For all-cause mortality at 6 or 12 months, the comparison between intervention and control was calculated as a risk ratio. Forest plots graphically summarize results of individual studies and of the pooled analysis (Appendix E).⁵⁴

The chi-squared statistic and the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity) were calculated to assess heterogeneity in effects between studies.^{55,56} An I^2 from 0 to 40 percent might not be important, 30 percent to 60 percent may represent moderate heterogeneity, 50 percent to 90 percent may represent substantial heterogeneity, and ≥ 75 percent represents considerable heterogeneity.⁵² The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g., p value from the chi-squared test, or a confidence interval for I^2). Whenever including a meta-analysis with considerable statistical heterogeneity in this report, we provide an explanation for doing so, considering the magnitude and direction of effects.⁵² We conducted sensitivity analyses for all analyses where considerable heterogeneity was present (i.e., I^2 statistic greater than 75 percent). Quantitative analyses were conducted using Stata[®] version 11.1 (StataCorp LP, College Station, TX) and Comprehensive Meta Analysis[®] version 2.2.055 (BioStat, Inc., Englewood, NJ).

Strength of the Body of Evidence

We graded the strength of evidence based on the guidance established for the Evidence-based Practice Center Program.⁵⁷ Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias.

Table 3 describes the grades of evidence that can be assigned. We graded the strength of evidence for mental health outcomes (KQ 1), chronic medical condition outcomes (KQ 2), and harms (KQ 3). Two reviewers assessed each domain for each key outcome and differences were resolved by consensus.

Table 3. Definitions of the grades of overall strength of evidence

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

*Owens et al., 2010⁵⁷

Applicability

We assessed applicability of the evidence following guidance from the *Methods Guide for Comparative Effectiveness Reviews*.⁵⁸ We used the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence included the following: ethnicity of enrolled populations, type of practice setting (open vs. closed), and use of interventions that may be difficult to incorporate into routine practice for many providers (e.g., they require substantial resources or time, or they may be delivered by research staff rather than existing staff in the practice).

Peer Review and Public Commentary

Experts in the field and individuals representing stakeholder and user communities were invited to provide external peer review of this CER. They were charged with commenting on the content, structure, and format of the evidence report, providing additional relevant citations, and pointing out issues related to how we conceptualized the topic and analyzed the evidence. Our Peer Reviewers (listed in the front matter) gave us permission to acknowledge their review of the draft. AHRQ staff and an associate editor also provided comments. In addition, the Scientific Resource Center posted the draft report on the AHRQ Web site (<http://effectivehealthcare.ahrq.gov/>) for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented everything in a “disposition of comments report” that will be made available 3 months after the Agency posts the final CER on the AHRQ Web site.

Results

Introduction

This chapter is organized by Key Question (KQ) and grouped by medical condition(s) when possible. Briefly, we wanted to examine the comparative effectiveness of practice-based interventions for primary care patients with concomitant mental health and chronic medical conditions; we focused on five main outcomes: mental health (KQ 1), chronic medical (KQ 2), harms of interventions (KQ 3), components of interventions (KQ 4), and characteristics of practice settings in which the interventions occurred (KQ 5). Our results pertain to the general adult population; no studies that met our inclusion criteria reported on young adults or pregnant women. Regarding older adults, one study⁵⁹⁻⁶³ selectively recruited for age 60 or older; however, participants across all studies in this review tended to be middle-aged or older (mean age, 59; range of means, 47 to 72) so we do not report results for older adults separately. Several studies reported on traditionally underrepresented populations, including women,⁶⁴⁻⁶⁶ Spanish speakers,⁶⁴⁻⁶⁷ and predominantly African-American male veterans with HIV;⁶⁸ we report these results in the context of overall results by medical condition, not in separate categories.

Results of Literature Searches

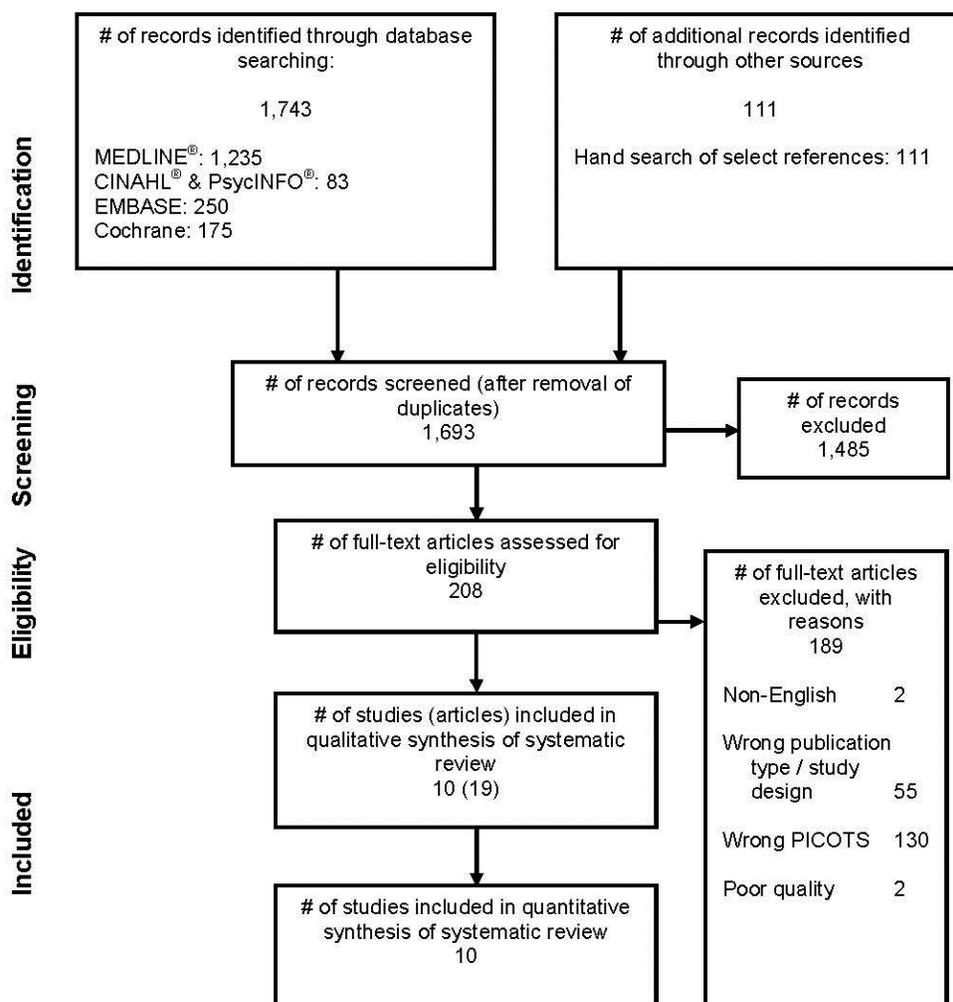
Results of our searches are presented in Figure 2. We ultimately included 19 published articles reporting on 10 randomized controlled trials (RCTs). We recorded the reason that each excluded full-text publication did not satisfy the eligibility criteria and compiled a comprehensive list of such studies (Appendix B). Evidence tables for included studies can be found in Appendix C.

Description of Included Studies

In the 10 included trials, sample sizes ranged from 55 to 1,001, and study duration ranged from 6 to 24 months. Nine trials were conducted in the United States (1 of these in Puerto Rico) and 1 in Scotland. All included studies characterized their respective intervention as a form of *collaborative care*, not another form of a practice-based intervention (such as integrated care). Similarly, all included studies specified *depression* as the targeted mental health condition; no studies specified anxiety as the condition of interest. Accordingly, we use the term depression, instead of mental health condition, when describing the results. The designated chronic medical conditions included arthritis,^{60, 63} cancer,^{59, 64, 66, 69} diabetes,^{37, 39, 61, 62, 65, 70-73} heart disease,⁷⁴ and HIV.⁶⁸ Two studies selected patients with one or more active medical conditions.^{67, 75}

The 19 articles represent 10 different studies. Five articles⁵⁹⁻⁶³ are secondary analyses from the Improving Mood—Promoting Access to Collaborative Treatment (IMPACT) trial;⁵ it tested a collaborative care depression intervention in older adult primary care patients, representing preplanned subgroups of patients with arthritis, cancer, and diabetes. Six articles^{37, 39, 70-73} are from the Pathways trial; it tested a collaborative care intervention in primary care patients with diabetes and depression. The majority of all studies reported their funding source as the government, and in some cases “multiple sources,” including foundations. All studies reported their funding source, and no study identified an industry sponsor.

Figure 2. Disposition of articles (PRISMA figure)



Source: Moher et al., 2009⁴⁵

Abbreviations: CINAHL, Cumulative Index to Nursing and Allied Health Literature; PICOTS, population, intervention, comparator, outcome, timing, setting; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Because all KQs draw from the same universe of evidence, we present the trials in two ways here as context for reading the remainder of results. Tables 4 through 9 display the characteristics of trials for the specific chronic medical conditions. Table 10 summarizes the main elements of the trial interventions and control groups. For IMPACT,⁵⁹⁻⁶³ Bypassing the Blues,⁷⁴ Symptom Management Research Trials (SMaRT) Oncology 1,⁶⁹ HITIDES (HIV Implementation of Translating Initiatives for Depression into Effective Solutions),⁶⁸ the Multifaceted Oncology Depression Program (MODP),⁶⁴ and Vera et al.,⁶⁷ the control condition was usual care, which consisted of informing patients of their depression status and advising them to share this information with their primary care provider (PCP).

Table 4. Characteristics of included trials of patients with arthritis

Author, Year Study Name Country Setting	N Duration (mths)	Mean Age (y) ^a	% Female ^a % Nonwhite ^a	Depression-Related Eligibility Requirement	
				Baseline Depression Score ^{a,b}	Quality
Lin et al., 2003, ⁶³	1,001	72.0 ^c	68.3	Major depression or dysthymia per	Fair
Lin et al., 2006 ⁶⁰	24		24	DSM-IV SCI	
IMPACT					
US				SCL-20: 1.7	
PC					

^a Overall mean as reported, range of means for treatment groups, or overall mean calculated using mean age from each treatment group.

^b See Table 11 for depression scale details.

^c The IMPACT trial enrolled only people ≥ 60 years of age.

Abbreviations: DSM, Diagnostic and Statistical Manual; IMPACT, Improving Mood—Promoting Access to Collaborative Treatment; mths, months; PC, primary care; SCI, structured clinical interview; SCL-20, Symptom Checklist—depression scale; US, United States; y, years.

Table 5. Characteristics of included trials of patients with cancer

Author, Year Study Name Country Setting	N Duration (mths)	Mean Age (y) ^a	% Female ^a % Nonwhite ^a	Depression-Related Eligibility Requirement	
				Baseline Depression Score ^{a,b}	Quality
Dwight-Johnson et al., 2005 ⁶⁴ MODP US PC-like	55 8	47.3	NR ^c	Major depression per PHQ-9 or dysthymia per PRIME-MD PHQ-9: 12.6-13.4	Fair
Ell et al., 2008 ⁶⁶ ADAPt-C US PC-like	472 12	~50 ^d	84.5 87.9	PHQ-9 ≥10 or dysthymia per DSM-IV SCI PHQ-9: 13.1	Fair
Fann et al., 2009 ⁵⁹ IMPACT US PC	215 24	71.8 ^e	60 25	Major depression or dysthymia per DSM-IV SCI SCL-20: 1.6	Fair
Strong et al., 2008 ⁶⁹ SMaRT Oncology 1 UK PC-like	200 12	56.6	69-72 NR	HADS ≥15 and major depression per DSM-IV SCI and SCL-20 ≥1.75 SCL-20: 2.3-2.4 (median)	Fair

^a Overall mean as reported, range of means for treatment groups, or overall mean calculated using mean age from each treatment group.

^b See Table 11 for depression scale details.

^c Race/ethnicity not reported, but 85–96 percent were Spanish-only speakers.

^d Age only reported as percent ≥50 yrs.

^e The IMPACT study enrolled only people ≥60 years old.

Abbreviations: ADAPt-C, Alleviating Depression Among Patients with Cancer; DSM, Diagnostic and Statistical Manual; HADS, Hospital Anxiety and Depression Scale; IMPACT, Improving Mood – Promoting Access to Collaborative Treatment; MODP, Multifaceted Oncology Depression Program; mths, months; NR, not reported; PC, primary care; PHQ-9, Patient Health Questionnaire – depression module; PRIME-MD, Primary Care Evaluation of Mental Disorders; SCI, structured clinical interview; SCL-20, Symptom Checklist – depression scale; SMaRT, Symptom Management Research Trials; UK, United Kingdom; US, United States; y, years.

Table 6. Characteristics of included trials of patients with diabetes

Author, Year Study Name Country Setting	N Duration (mths)	Mean Age (y) ^a	% Female ^a % Nonwhite ^a	Depression-Related Eligibility Requirement	
				Baseline Depression Score ^{a,b}	Quality
Ell et al., 2010 ⁶⁵ MDDP US PC and PC-like	387 18	NR ^c	79.8-84.5 96.5	PHQ-9 ≥10 SCL-20: 1.4-1.7	Fair
Ciechanowski et al., 2006; ³⁹ Katon et al., 2008; ⁷⁰ Katon et al., 2004; ³⁷ Kinder et al., 2006; ⁷¹ Lin et al., 2006; ⁷² Simon et al., 2007; ⁷³ Pathways US PC	329 60	58.4	64.8-65.2 32-49	PHQ-9 ≥10 and SCL-20 ≥1.1 SCL-20: 1.63-1.71	Fair
Williams et al., 2004 ⁶² ; Katon et al., 2006 ⁶¹ IMPACT US PC	417 24	70.2 ^c	53-54 35-37	Major depression or dysthymia per DSM-IV SCI SCL-20: 1.67-1.72	Fair

^a Overall mean as reported, range of means for treatment groups, or overall mean calculated using mean age from each treatment group.

^b See Table 11 for depression scale details.

^c Age only reported as percent ≥50 yrs; 69 percent-75 percent were ≥50 yrs.

Abbreviations: DSM, Diagnostic and Statistical Manual; IMPACT, Improving Mood – Promoting Access to Collaborative Treatment; MDDP, Multifaceted Diabetes and Depression Program; mths, months; NR, not reported; PC, primary care; PHQ-9, Patient Health Questionnaire – depression module; SCI, structured clinical interview; SCL-20, Symptom Checklist – depression scale; US, United States; y, years.

Table 7. Characteristics of included trials of patients with heart disease

Author, Year Study Name Country Setting	N Duration (mths)	Mean Age (y) ^a	% Female ^a % Nonwhite ^a	Depression-Related Eligibility Requirement	
				Baseline Depression Score ^{a,b}	Quality
Rollman et al., 2009 ⁷⁴	302 8	64.0	37-46 7-12	PHQ-9 ≥11	Good
Bypassing the Blues US Unclear ^c				PHQ-9: 13.5-13.6 HRSD: 15.9-16.5	

^a Overall mean as reported, range of means for treatment groups, or overall mean calculated using mean age from each treatment group.

^b See Table 11 for depression scale details.

^c Patients were recruited before hospital discharge; intervention took place over the telephone.

Abbreviations: HRSD, Hamilton Rating Scale for Depression; mths, months; PHQ-9, Patient Health Questionnaire – depression module; US, United States; y, years.

Table 8. Characteristics of included trials of patients with HIV

Author, Year Study Name Country Setting	N Duration (mths)	Mean Age (y) ^a	% Female ^a % Non-White ^a	Depression-Related Eligibility Requirement	
				Baseline Depression Score ^{a,b}	Quality
Pyne et al., 2011 ⁶⁸	276	49.8	3-4	PHQ-9 ≥10	Good
HITIDES US PC-like	12		77-78	PHQ-9: 15.7-16.0 SCL-20: 1.8-1.9	

^a Overall mean as reported, range of means for treatment groups, or overall mean calculated using mean age from each treatment group.

^b See Table 11 for depression scale details.

Abbreviations: HITIDES, HIV Implementation of Translating Initiatives for Depression into Effective Solutions; mths, months; PC, primary care; PHQ-9, Patient Health Questionnaire – depression module; SCL-20, Symptom Checklist – depression scale; US, United States; y, years.

Table 9. Characteristics of included trials of patients with multiple conditions

Author, Year Study Name Country Setting	N Duration (mths)	Mean Age (y) ^a	% Female ^a % Nonwhite ^a	Depression-Related Eligibility Requirement	
				Baseline Depression Score ^{a,b}	Quality
Katon et al., 2010 ⁷⁵ TEAMcare ^c US PC	214 12	56.9	48-56 22-25	PHQ-9 ≥10 PHQ-9: 13.9-14.7 SCL-20: 1.7	Fair
Vera et al., 2010 ⁶⁷ None US (Puerto Rico) PC	179 6	55.2	76 100	PHQ-9 (cutoff NR) and SCL- 20 >1.0 SCL-20: 2.3	Good

^a Overall mean as reported, range of means for treatment groups, or overall mean calculated using mean age from each treatment group.

^b See Table 11 for depression scale details.

^c Diabetes and/or heart disease.

Abbreviations: mths, months; PC, primary care; PHQ-9, Patient Health Questionnaire—depression module; SCL-20, Symptom Checklist—depression scale; US, United States; y, years.

Table 10. Summary of collaborative care intervention trials

Author/ Trial Name Disease	Intervention Summary	Delivery Method	
		Delivered By	Control Condition ^a
		Psychiatrist Supervision?	
Lin et al., 2003; ⁶³ Lin et al., 2006; ⁶⁰ Fann et al., 2009; ⁵⁹ Williams et al., 2004; ⁶² Katon et al., 2006 ⁶¹ IMPACT Arthritis, cancer, diabetes	Care management based on stepped care treatment algorithm; patient preference for treatment: antidepressants or problem-solving therapy (6–8 sessions); monitoring of treatment response	In-person and telephone Depression care specialist (nurse or clinical psychologist) Yes	Usual care
Dwight-Johnson et al., 2005 ⁶⁴ MODP Cancer	Described as being based on the IMPACT model	In-person and telephone Bilingual cancer depression care specialist (master's level social worker) Yes	Usual care
Ell et al., 2008 ⁶⁶ ADAPT-C Cancer	Described as being based on the IMPACT model	In-person and telephone Bilingual cancer depression care specialist (master's level social worker) Yes	Enhanced usual care
Ell et al., 2010 ⁶⁵ MDDP Diabetes	Described as being based on the IMPACT model	In-person and telephone Bilingual diabetes depression care specialist (master's level social worker) Yes	Enhanced usual care
Ciechanowski et al., 2006; ³⁹ Katon et al., 2008; ⁷⁰ Katon et al., 2004; ³⁷ Kinder et al., 2006; ⁷¹ Lin et al., 2006; ⁷² Simon et al., 2007 ⁷³ Pathways Diabetes	Described as being based on the IMPACT model	In-person and telephone Depression clinical specialist (nurse) Yes	Enhanced usual care
Katon et al., 2010 ⁷⁵ TEAMcare Diabetes +/- heart disease	Support for self-care of depression (including pharmacotherapy) and individualized goal-setting; treat-to-target program for DM and/or CHD; motivational coaching; maintenance support	In-person and telephone Medically supervised nurse trained in diabetes education Yes	Enhanced usual care

Table 10. Summary of collaborative care intervention trials (continued)

Author/Trial Name Disease	Intervention Summary	Delivery Method	
		Delivered By	Control Condition ^a
		Psychiatrist Supervision?	
Pyne et al., 2011 ⁶⁸ HITIDES HIV	Stepped care approach; education/activation; recommendations for medications and/or mental specialty referral; web-based decision support	Telephone Off-site depression care team: nurse depression care manager, pharmacist, psychiatrist Yes	Usual care
Rollman et al., 2009 ⁷⁴ Bypassing the Blues Heart disease	Education on depression and CHD; support to PCP on antidepressants; referral to mental health specialists as needed; phone monitoring for symptoms	Telephone Nurse care manager Yes	Usual care
Strong et al., 2008 ^{69, b} SMaRT Oncology 1 Cancer	Manual-Based Depression Care for People with Cancer; up to 10 sessions of problem-solving treatment to address coping; progress monitored by telephone; advice on choice of antidepressant if requested	In-person and telephone Nurses with no psychiatry experience Yes	Usual care
Vera et al., 2010 ⁶⁷ NA ≥1 of the following: diabetes, hypothyroidism, asthma, hypertension, chronic bronchitis, arthritis, heart disease, high cholesterol, stroke	Depression education; antidepressant medications and/or 13 sessions of cognitive behavioral therapy	In-person and telephone Master's level counselor or psychologist Yes	Usual care

^aSpecific components of usual care and enhanced usual care are listed in Appendix C.

^bStudy took place in the United Kingdom where both primary care and mental health specialty services are free at the point of delivery.

Abbreviations: ADAPt-C, Alleviating Depression Among Patients with Cancer; CHD, coronary heart disease; DM, diabetes mellitus; IMPACT, Improving Mood—Promoting Access to Collaborative Treatment; MDDP, Multifaceted Diabetes and Depression Program; PCP, primary care provider.

By contrast, ADAPt-C,⁶⁶ Pathways,^{37, 39, 70, 71, 73} TEAMcare,⁷⁵ and the Multifaceted Diabetes and Depression Program (MDDP)⁶⁵ compared collaborative care with enhanced usual care, which extended usual care by including some degree of additional communication between the research staff or diabetes care manager and the patient's PCP and/or family about the patient's depression status.

Key Question 1a: Intermediate mental health outcomes and satisfaction with care

In the key points below, we summarize the main findings by outcome and report the strength of evidence (SOE) for each outcome. The populations for the included studies all had depression identified as their mental health condition.

Key Points

- Collaborative care interventions achieved greater depression symptom improvement than usual care, based on eight RCTs and two RCT subgroup analyses (standardized mean difference [SMD], 0.45; 95% confidence interval [CI], 0.29 to 0.61 at 6 months; SMD 0.47, 95% CI, 0.29 to 0.65 at 12 months) (moderate SOE).
- Collaborative care interventions achieved higher rates of depression response (≥ 50 percent reduction in symptoms from baseline) than usual care, based on eight RCTs and two RCT subgroup analyses (number needed to treat [NNT]), 5 at 6 months; NNT, 6 at 12 months) (moderate SOE).
- Collaborative care interventions resulted in more depression-free days at 12 months than usual care in the four studies that measured the outcome (range of differences between intervention and control groups: 17 to 54 days (moderate SOE).
- Results consistently favored collaborative care interventions across all medical conditions.
- Remission of depression favored collaborative care over usual care at 6 months and at 12 months (but less so) based on three RCTs and two RCT subgroup analyses (NNT, 8 at 6 months; NNT, 12.5 at 12 months) (moderate SOE).
- No study addressed recurrence as an outcome.
- Evidence was insufficient to draw conclusions about the effect of collaborative care interventions on adherence to antidepressants.
- Collaborative care interventions received significantly higher ratings of patient satisfaction than usual care as reported in three RCTs and one RCT subgroup analysis, including patients with diabetes, heart disease, and cancer (moderate SOE).

Detailed Synthesis

Depression Symptom Improvement and Treatment Response

All included studies examined depression symptom improvement or depression treatment response (≥ 50 percent reduction in depression score), or both, at 6 and 12 months. Seven studies^{37, 59-63, 65, 67-69, 75} used the Symptom Checklist-20,⁷⁶ two^{64, 66} used the Patient Health Questionnaire-9,⁷⁷ and one⁷⁴ used the Hamilton Rating Scale for Depression⁷⁸ (Table 11).

Table 11. Instruments used to measure depressive symptoms, response, and remission

Abbreviated Name	Complete Name of Measure or Instrument	Range of Scores	Improvement Denoted by	Notes
HRSD17 ^a	Hamilton Rating Scale for Depression – 17 item	0-52	Decrease	Observer-rated
PHQ-9	Patient Health Questionnaire – 9 item	0-27	Decrease	Self-rated
SCL-20 (HSCL-20)	(Hopkins) Symptom Checklist – 20 item	0.0-4.0	Decrease	Self-rated

^a Also referred to as the HAM-D¹⁷ and the HDRS.¹⁷

Abbreviations: HAM-D, Hamilton Rating Scale for Depression; HDRS, Hamilton Depression Rating Scale; HSCL, Hopkins Symptom Checklist; HRSD, Hamilton Rating Scale for Depression; PHQ, Patient Health Questionnaire; SCL, Symptoms Checklist Depression.

Quantitative analyses and strength of evidence data are detailed in Appendix E and Appendix F, respectively. All studies favored a collaborative care intervention versus usual care on depression outcomes at all time points.

For the intermediate outcome of improvement in depression symptoms, Table 12 reports results of meta-analyses from 6 and 12 months. Results from studies that used the Symptoms Checklist Depression-20 (SCL-20) are reported using weighted mean differences (WMD). Results that include studies using any measure of depression symptoms are reported using SMD values.

The magnitude of effect did not differ appreciably. Subjects receiving collaborative care interventions had a 0.38 greater improvement on SCL-20 at both 6 and 12 months than those in control groups. Given that the range of the SCL-20 is 0 to 4 (lower scores meaning less depression), this magnitude of change is generally considered a clinically important difference.^{79, 80}

Table 12. Summary of meta-analyses for intermediate outcomes for practice-based interventions aimed at improving the mental health condition or both the mental health and chronic medical conditions compared with controls

Outcome	Timing	N Studies	Statistic	Effect Size	95% CI	I ²
Depression symptoms	6 months	5	WMD	0.38	0.24 to 0.51	66.94
Depression symptoms	6 months	7	SMD	0.45	0.29 to 0.61	64.52
Depression symptoms	12 months	5	WMD	0.38	0.30 to 0.46	1.09
Depression symptoms	12 months	6	SMD	0.47	0.29 to 0.65	68.55
Response ^a	6 months	9	RD	0.20	0.14 to 0.26	54.66
Response ^a	12 months	7	RD	0.17	0.12 to 0.23	50.95
Remission ^b	6 months	3	RD	0.12	0.06 to 0.18	0.00
Remission ^b	12 months	3	RD	0.08	0.02 to 0.14	0.00
Treatment satisfaction	12 months	4	RD	0.21	0.11 to 0.30	69.62

^a Response indicated by ≥ 50 percent reduction in symptom score.

^b Remission indicated by a Symptom Checklist-20 score <0.5 .

Abbreviations: CI, confidence interval; RD, risk difference; SMD, standardized mean difference; WMD, weighted mean difference.

We pooled data from nine studies to assess response at 6 and 12 months (Table 12). At 6 months, 20 percent more subjects receiving collaborative care achieved response (50 percent reduction in mental health score) than did subjects in control groups. The TEAMcare study⁷⁵ reported a significantly higher percentage difference in those achieving response at 6 months than in those with usual care (0.36; 95% CI, 0.23 to 0.49); a sensitivity analysis removing that study slightly reduced that number to 17 percent more subjects achieving response compared with subjects in control groups. From these data, we calculated an NNT to achieve response at 12 months of six patients. Despite significantly greater improvement among intervention participants than among controls on measures of depression, a large proportion of patients remained symptomatic. For example, the range among intervention arms of patients reporting response at 6 months (≥ 50 percent reduction in depression score from baseline) was 37 percent to 59 percent (Appendix E).

For patients with diabetes in the Pathways trial,³⁷ additional analyses showed that patients with two or more diabetic complications were significantly more likely than usual care patients to experience reductions in depressive symptoms; patients with fewer than two complications showed no difference between arms.⁷¹ When investigators stratified the participants in the

Pathways trial by independent versus interactive relationship styles, depression outcomes improved more significantly compared with usual care in patients with an independent attachment style.³⁹ These isolated analyses lend context for interpreting the findings in diabetic patients, but they are insufficient to draw quantitative conclusions.

Depression-Free Days

Four studies reported depression-free days.^{37, 59-63, 68} The cancer subgroup of IMPACT⁵⁹ reported 51 more depression-free days in the intervention subjects than in the usual care subjects at 12 months (186 vs. 135, $p < 0.001$); in the diabetes subgroup,⁶¹ subjects receiving collaborative care had 59 more depression-free days at 1 year than controls (95% CI, 37 to 91). In the Pathways project,⁷³ subjects in the intervention arm had 20 more depression-free days at 12 months than controls (186 vs. 166; 95% CI, -2 to 42). The HIV study⁶⁸ reported an adjusted mean difference of 19 days (95% CI, 11 to 28) at 12 months.

Remission and Recurrence

We pooled data from three trials in meta-analyses of remission of depression in patients with diabetes, HIV, and cancer at 6 and 12 months (Table 12 and Appendix E).^{59, 66, 68} By 6 months, 12 percent fewer subjects in control groups than patients in intervention groups achieved remission (RD, 0.12; 95% CI, 0.06 to 0.18). From this, we calculated an NNT of 8 patients to achieve one remission. Although results continued to favor the intervention group at 12 months, the NNT to achieve one remission was 12.5.

Two trials that reported on remission were not amenable to meta-analysis. The ADAPt-C study of predominantly female Hispanic patients with cancer used the PHQ-9.⁶⁶ These investigators reported that 70 percent of intervention patients were in remission at 6 months, with remission defined as “no longer had major depression”; conclusions cannot be drawn in the absence of comparator data. In the arthritis subgroup of IMPACT, Lin et al. reported that 24 percent of intervention patients and 38 percent of usual care patients met DSM-IV criteria for depression at 6 months ($t, -4.6$; $p < 0.001$).⁶³

No trial examined recurrence of depression.

Satisfaction With Treatment

Six trials addressed patient satisfaction with mental health treatment, although two assessed only the intervention group.^{66, 69} Four studies were suitable for meta-analysis; all four favored the intervention group across patients with diabetes,^{62, 64} diabetes and/or heart disease,⁷⁵ and cancer.⁵⁹ Our meta-analysis found that 21 percent more subjects receiving collaborative care than controls were satisfied with treatment (Table 12 and Appendix E). In those trials, treatment satisfaction was defined as follows: care rated “satisfied” to “very satisfied” (MDDP); care rated “moderately satisfied” to “very satisfied” (Pathways); care rated “very satisfied” to “extremely satisfied” (TEAMcare); and care rated “good” or “excellent” (IMPACT).

Treatment Adherence

Two trials reported on the outcome of adherence to antidepressant medications; we could not draw meaningful conclusions from this small amount of evidence. The Pathways study of diabetics showed significantly greater adherence in the collaborative care group, reporting a 6-month adjusted odds ratio (OR) of 2.29 (95% CI, 1.38 to 3.82) and a 12-month adjusted OR of

2.18 (95% CI, 1.32 to 3.62).³⁷ The HITIDES (HIV) study showed no difference between treatment groups at 6 months, with an OR of 1.65 (95% CI, 0.75 to 3.62). At 12 months, the direction of effect was reversed but remained statistically insignificant (OR, 0.56; 95% CI, 0.20 to 1.57).⁶⁸

We found no other measures of adherence relevant to intermediate mental health outcomes.

Applicability

These findings are generally applicable to primary care patients with depression (we found no studies of anxiety) and at least one chronic medical condition, but they may not apply to patients with medical conditions not addressed in this report. The average age across studies was 59, an age group most likely to have chronic disease; thus, the relevance of these results to either young adults with chronic disease or more elderly patients who may have multiple disorders remains unclear. (IMPACT included only adults ≥ 60 years of age, but the average age was 71.⁵) People of Hispanic origin (predominantly female)⁶⁴⁻⁶⁶ and male veterans⁶⁸ were represented and appeared to respond similarly across outcomes, but we had too few data on such patients to analyze separately.

Included trials used clinically meaningful measures and had study durations (at least 6 months) that provided a real-world context. Although these trials represented several types of settings, including primary care–like cancer and HIV clinics, they all had in common a care manager who directed the intervention. The intermediate mental health outcomes achieved here might, therefore, apply only to settings in which such services and personnel can be accommodated and afforded. Similarly, practices that agreed to participate in these trials may reflect a selection bias based on culture and willingness to collaborate.

Key Question 1b: Other mental health–related outcomes

In the key points below, we summarize the main findings by outcome and report the SOE for each outcome. For this KQ, outcomes of interest include suicide, use of antidepressants, mental health–related quality of life, use of mental health care, sick days attributable to mental health, and employment stability.

Key Points

- Evidence was insufficient to draw conclusions about suicide; one suicide was reported in a usual care group.
- Collaborative care interventions generally resulted in greater antidepressant use than usual care at 6 and 12 months (RD, 0.22; 95% CI, 0.13 to 0.32 at 12 months) (low SOE).
- Patients in collaborative care intervention arms achieved greater mental health–related quality of life than usual care at 6 and 12 months using the mental component of the Medical Outcomes Study Short Form (WMD, 2.98; 95% CI, 1.41 to 4.56 at 12 months) (moderate SOE).
- Four studies reported on use of mental health services; each showed greater use of any services at 6 and/or 12 months (42 percent to 97 percent vs. 16 percent to 57 percent for intervention and control groups, respectively) (low SOE).
- Evidence was insufficient (no data from any trial) on sick days or employment stability.

Detailed Synthesis

Suicide

Two studies reported suicide-related outcomes. Authors of the MODP reported that they were unaware of any attempted or completed suicides in either treatment group.⁶⁶ Strong et al. reported one suicide in the usual care group.⁶⁹ Data were too sparse to permit conclusions for this outcome.

Use of Antidepressants

Three studies examined antidepressant use at 6 months in patients with HIV,⁶⁸ heart disease,⁷⁴ and cancer.⁵⁹ Meta-analysis indicated greater use in the intervention group in a pooled analysis of the data (Table 13 and Appendix E). Nine percent more collaborative care patients than usual care subjects were using antidepressants (95% CI, -0.02 to 0.12). Five articles reported use of antidepressants at 12 months, including additional populations with diabetes⁶⁵ and arthritis.⁶² Our meta-analysis indicated greater use in the intervention arms, but heterogeneity was considerable (I^2 , 77.98) (Appendix E). The one study that did not find greater use of antidepressants for those in the intervention group was the HIV study, HITIDES.⁶⁸ Because patients with HIV may differ from patients with other chronic diseases in ways that could affect medication use, we ran a sensitivity analysis, removing the HITIDES results. This analysis resulted in less heterogeneity (I^2 , 65.37; RD, 0.22; 95% CI, 0.13 to 0.32) and an overall NNT of 4.5 (Appendix E).

Table 13. Summary of meta-analyses for other mental health–related outcomes

Outcome	Timing	N Studies	Statistic	Effect Size	95% CI	I^2
Use of antidepressants	6 months	3	Risk difference	0.09	-0.02 to 0.12	54.22
Use of antidepressants	12 months	4 ^a	Risk difference	0.22	0.13 to 0.32	65.37
Self-rated mental health-related QOL ^b	6 months	3	SMD	0.31	0.16 to 0.45	35.31
Self-rated mental health-related QOL ^c	6 months	4	WMD	3.62	1.30 to 5.94	61.53
Self-rated mental health-related QOL ^c	12 months	4	WMD	2.98	1.41 to 4.56	41.78

^a Results of the meta-analysis that excluded the HIV Implementation of Translating Initiatives for Depression into Effective Solutions (HITIDES) study because of high heterogeneity.

^b Self-rated mental health was measured with the 12-item Short Form Survey from the RAND Medical Outcomes Study (SF-12) for all trials except Bypassing the Blues, which used the SF-36. The Bypassing the Blues data were from the 8-month endpoint.

^c Self-rated mental health is measured with the 12-item Short Form Survey from the RAND Medical Outcomes Study (SF-12) for all trials.

Abbreviations: CI, confidence interval, rounded to tenths; QOL, quality of life; SMD, standardized mean difference; WMD, weighted mean difference.

Mental Health–Related Quality of Life

Five studies measured well-being using the mental component of Medical Outcomes Study Short Form.^{62, 65, 66, 68, 74} Four studies used the 12-item instrument (Short Form Health Survey [SF-12]),^{4, 15, 17, 19} one used the 36-item (SF-36).⁷⁴ We conducted a meta-analysis across conditions, combining studies of subjects with depression and one chronic disorder (cancer, diabetes, heart disease, or HIV). Our meta-analysis favored collaborative care interventions over controls at both 6 and 12 months (Table 13 and Appendix E). Only the HIV study did not find a

statistically significant difference between intervention and control groups at either time point, but point estimates favored the intervention group.⁶⁸

Use of Mental Health Services

Four articles reported on this outcome. Ell et al., in their diabetic sample, showed that intervention patients received any depression treatment more often than controls at 12 and 18 months (83.9 percent vs. 32.5 percent and 45.8 percent vs. 24.1 percent, respectively, both $p < 0.001$).⁶⁵ In the Puerto Rico trial of patients with one or more medical conditions, significantly more intervention patients received any depression treatment at 6 months (97 percent vs. 57 percent, p not reported).⁶⁷ Data from the IMPACT trial showed that patients with arthritis in the intervention group were more likely to receive mental health services at 12 months than patients in the control group (47 percent vs. 16 percent, $p < 0.001$);⁶³ similarly for the sample with cancer,⁵⁹ service use favored the intervention group at 6 and 12 months (percentage with any mental health visit in the past 3 months: 40 vs. 15 and 42 vs. 16, respectively, both $p < 0.001$), but the difference was no longer statistically significant at 18 months (15 vs. 12, $p = 0.56$). The association with more depression treatment in the intervention group was consistent across all trials that reported on this outcome.

Sick Days Related to Mental Health

No data on sick days related to mental health were reported.

Employment Stability

No data on employment stability were reported.

Applicability

We refer to the applicability section in KQ 1a for the same consideration of constraints posed by these types of studies. In general, the results in this section apply to primary care patients with depression and one or more chronic medical conditions, receiving care in a setting where a care manager is available to coordinate care. These results must be considered in the context of heterogeneity across medical conditions and interventions.

Key Question 2a: Intermediate chronic medical outcomes

For this Key Question, we were interested in the effects of practice-based interventions on medical outcomes related to the specified chronic medical condition(s). Of the trials that met our inclusion criteria, the medical conditions included arthritis, diabetes, cancer, heart disease, HIV, and one or more conditions. Outcomes of interest include symptom improvement, response to treatment, treatment adherence, and satisfaction with care. We summarize the main findings by medical condition and report the SOE for each outcome.

Key Points

- Few studies reported specifically on symptom improvement; data were reported for people with arthritis,^{60, 63} diabetes,⁶⁵ and HIV.⁶⁸ Evidence was insufficient to reach conclusions for this outcome.

- Hemoglobin A1c (HbA1c) was reported as a measure of response in four studies of diabetic patients. Our meta-analysis found no between-group differences for change in HbA1c (WMD, 0.13; 95% CI, -0.55 to 0.41 at 6 months; WMD, 0.24; 95% CI, -0.14 to 0.62 at 12 months) (low SOE).
 - The TEAMcare trial may serve as an exception because of its design and because it was the only study to use HbA1c as a predefined outcome measure;⁷⁵ it reported significant differences in HbA1c (intervention vs. control): 8.14 vs. 8.04 at baseline; 7.42 vs. 7.87 at 6 months; and 7.33 vs. 7.81 at 12 months; overall $p < 0.001$. At 12 months, 37 intervention subjects vs. 18 controls achieved a ≥ 1.0 percent improvement (response) in HbA1c ($p = 0.006$).
- Treatment adherence was reported for cancer,⁶⁴ diabetes,^{62, 72, 75} and HIV,⁶⁸ but only diabetes provided data from more than one study.
 - Diabetes and diet: patients receiving the collaborative care intervention were no more likely than controls to adhere to a generally healthy diet in three of three trials (moderate SOE).
 - Diabetes and exercise: patients receiving the collaborative care intervention were more likely than controls to adhere to an exercise program in two of three trials (low SOE).
 - Diabetes and medications: Based on mixed results from two studies, evidence was insufficient to draw a conclusion.
- Evidence was insufficient to draw conclusions about treatment satisfaction.

Detailed Synthesis

Symptom Improvement

Arthritis

One study, the IMPACT subgroup analysis of subjects with arthritis,⁶³ reported data on arthritis pain based on a 10-point severity scale (10 being worse). The intervention group reported a lower pain score compared with the control group at 6 months (-0.21; 95% CI, -0.6 to 0.19) and at 12 months (-0.53; 95% CI, -0.92 to -0.14), but arguably did not reflect clinically meaningful change at less than a 1-point difference. In a separate analysis,⁶⁰ baseline pain severity showed significant interactions with the intervention on 12-month pain severity ($p = 0.04$), revealing that the intervention was more effective than usual care in decreasing pain severity only in those with lower initial pain severity, but the difference between groups at 12 months was modest (intervention=4.54; control=5.41; change scores from baseline in each group not reported).

Cancer

No trial reported on cancer-related symptom improvement.

Cardiovascular Disease

No trial reported on heart disease-related symptom improvement.

Diabetes

The Ell et al. trial of predominantly Hispanic patients reported directly on diabetes symptoms using the Whitty-9 instrument,⁸¹ but it did not define a clinically meaningful important difference.⁶⁵ Intervention subjects had a lower symptom score at 6 months (1.65 vs. 1.79, $p=0.07$), but they were similar to controls at 12 months (1.66 vs. 1.69, $p=0.18$) and 18 months (1.79 vs. 1.74, $p=0.85$).

HIV

The Pyne et al. trial,⁶⁸ in a population of predominantly male veterans, used the 20-item Symptoms Distress Module⁸² to measure the severity of common HIV symptoms. Bothersome symptoms were defined as scores of three or four on a Likert-type scale, and the total number of bothersome symptoms was reported. The authors reported significant adjusted intervention effects versus controls at 6 months (beta, -2.6; 95% CI, -3.5 to -1.8; $p=0.03$) but not 12 months (beta, -0.9, 95% CI, -1.58 to 1.40, $p=0.88$).

Response

Arthritis

No trial reported on response to arthritis treatment, other than the study assessing pain severity described in the previous section on symptoms.

Cancer

No trial reported on cancer response.

Cardiovascular Disease

The TEAMcare trial of patients with depression and diabetes and/or heart disease reported that intervention subjects had a greater reduction in low-density lipoprotein than usual care subjects at 12 months (intervention at baseline=107, at 12 months=92; control at baseline=109, at 12 months=101; mean difference at 12 months=-9.1; 95% CI, -17.5 to -0.8).⁷⁵ The investigators also reported that intervention subjects had a 4.6-point (95% CI, 1.9 to 7.3) greater reduction in systolic blood pressure (SBP) than usual care subjects at 12 months (baseline SBP=136 and 132 in the intervention and control groups, respectively). Response was defined as an SBP ≥ 10 mm Hg decrease from baseline. At 12 months, 41 intervention subjects and 25 controls achieved response ($p=0.016$) from an overall sample of 214.

Diabetes

The TEAMcare trial defined response for HbA1c as a reduction of ≥ 1 percent from baseline.⁷⁵ At 12 months, 37 intervention subjects and 18 controls achieved response ($p=0.006$) from an overall sample of 214. They also reported a greater percentage of intervention subjects than control subjects reaching American Diabetes Association guideline targets for HbA1c, (LDL, and SBP at 12 months (16.3 vs. 12.5, p not reported).

Our meta-analysis using three of the four trials reporting HbA1c revealed no significant difference between intervention and control groups at 6 and 12 months (Table 14 and Appendix E). Among these, the TEAMcare study was the only study to report statistically significant differences in HbA1c for intervention patients compared with control patients: 8.14 versus 8.04 at baseline; 7.42 versus 7.87 at 6 months; and 7.33 versus 7.81 at 12 months; overall $p<0.001$.⁷⁵

Importantly, the nature and design of this trial differed from others in this CER because the investigators set out to provide coordinated care management and “treat-to-target” principles for patients with poorly controlled diabetes, coronary heart disease, or both, and coexisting depression. None of the other trials intended to use HbA1c as a primary outcome. We could not include the Pathways study in our meta-analyses because it lacked sufficient data on differences between arms, but the investigators reported no statistically significant group differences at baseline or 6 or 12 months.³⁷ They did report that HbA1c levels decreased over time across groups: mean=7.99 percent (standard deviation [SD], 1.47 percent) at baseline; mean=7.58 percent (SD, 1.47 percent) at 6 months; and mean=7.64 percent (SD, 1.57 percent) at 12 months.

Table 14. Summary of meta-analyses for intermediate chronic medical outcomes

Outcome	Timing	N Studies	Statistic	Effect Size	95% CI	I ²
Change in HbA1c	6 months	3	WMD	0.13	-0.55 to 0.41	45.52
Change in HbA1c	12 months	3	WMD	0.24	-0.14 to 0.62	67.79

Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c; WMD, weighted mean difference.

HIV

No trial reported on response.

Treatment Adherence

Arthritis

No trial reported on adherence to arthritis treatment.

Cancer

Of the three included trials involving cancer patients, only the MODP program⁶⁴ reported on adherence; the investigators defined this as “completing all doctor-recommended treatment or follow-up visits.” Intervention patients (89 percent) were more likely than usual care patients (70 percent) to be adherent at 8 months (OR 3.51; 95% CI, 0.82 to 15.03).

Diabetes

Three trials reported in different ways on adherence to diet and exercise,^{62, 72, 75} and two reported on adherence to standard diabetes medications^{62, 72} (Appendix C). Other measures of self-care were reported infrequently (such as foot care) and are detailed in the evidence tables (Appendix C).

Diet

A further analysis from the Pathways study reported the number of days in 1 week that the patient followed a generally healthy diet;⁷² by 12 months this outcome had risen by nearly 1 day in both groups (baseline mean 3.7 days/week for both groups). The two groups did not differ at 6 or 12 months (12-month mean 4.5 days/week for both groups). TEAMcare investigators reported the percentage adhering to a general diet plan ≥ 2 days per week; this outcome also showed no statistical difference at 12 months (68 percent intervention vs. 63 percent control, $p=0.37$).⁷⁵ The IMPACT diabetes analysis revealed a similar trend for patients reporting how well they followed their diet plan (ranked from 1 [always] to 5 [never]); scores were 2.57 (intervention) and 2.54 (control) at 12 months (mean adjusted difference -0.26, 95% CI, -0.65 to 0.12).⁶²

Exercise

From the Pathways cohort, Lin et al. reported no difference at any time points for the number of days in the last week spent exercising 30 or more minutes (Appendix C) and no significant improvement from baseline in either group (2.6 vs. 2.3 days at baseline; 2.7 vs. 2.6 at 12 months).⁷² TEAMcare researchers reported that 54 percent of intervention subjects versus 44 percent of controls adhered to a specific exercise routine ≥ 2 days per week ($p=0.21$).⁷⁵ In the IMPACT diabetes sample,⁶² patients in the intervention group performed significantly more exercise than those in the control group at 12 months (mean difference 0.50 day; $p=0.01$).

Medications

The Pathways researchers evaluated a subsample of participants⁷² for medication *nonadherence* to oral hypoglycemic medications, lipid-lowering agents, and angiotensin-converting enzyme inhibitors based on computerized records of pharmacy refills. Baseline and follow-up data revealed rates of nonadherence that ranged from 20 percent to 30 percent overall; these rates did not significantly change, nor did they differ, among treatment groups for lipid-lowering agents and angiotensin-converting enzyme inhibitors at 12 months (Appendix C). Interestingly, the rate of nonadherence to oral hypoglycemics was significantly higher in the intervention group than the control group at 12 months (28.2 vs. 24 percent, $p<0.03$).

The IMPACT investigators asked how often participants took their prescribed medications, scored on a scale from 1 [always] to 5 [never].⁶² They reported no significant difference over time and no differences between groups at any time points. At 12 months, the scores were 1.16 for the intervention group and 1.19 for the control group.

HIV

The HITIDES study defined patients as adherent to the HIV medication regimen when the number of pills taken over the past 4 days divided by the number prescribed was ≥ 95 percent.⁶⁸ The groups did not differ at either 6 months (74 percent vs. 72 percent, $p=0.65$) or 12 months (68 percent vs. 64 percent, $p=0.89$) (Appendix C).

Satisfaction With Care

TEAMcare asked subjects about their satisfaction with care of diabetes, heart disease, or both. At 12 months, 86 percent and 70 percent of patients in the intervention and control groups, respectively, reported being satisfied with their care.⁷⁵

Applicability

We refer to the applicability section in KQ 1a for the same consideration of constraints posed by these types of studies, specifically the required presence of a care manager to carry out the intervention. In general, the results in this section apply to a primary care population with depression and one of the chronic medical conditions discussed here, mostly patients with diabetes. Relatively few data were available on outcomes for patients with arthritis, cancer, heart disease, and HIV.

Key Question 2b: General health outcomes and costs of intervention

For this Key Question, we were interested in the effects of the collaborative care intervention on general health outcomes and costs of the intervention. General health outcomes of interest

include condition-specific morbidity, mortality, health care utilization, and quality of life. We summarize the main findings by outcome and report the strength of evidence for each outcome.

Key Points

- Evidence was insufficient to draw conclusions about morbidity related to the medical condition. In one arthritis trial, the intervention group had less pain interference (between group difference -0.56; 95% CI, -0.96 to -0.16 at 6 months, and -0.59; 95% CI, -1.00 to -0.19 at 12 months). In one trial of post-coronary artery bypass graft (CABG) patients, the intervention group had greater cardiac-related functioning (overall difference 4.6; 95% CI, 1.9 to 7.3; $p=0.001$; when stratified by sex, significant only in men).
- Eight trials reported on mortality. Few deaths were reported overall (most in cancer studies). Intervention and control subjects did not differ in mortality at 6 months (risk difference=0.00; 95% CI, -0.02 to 0.02) or 12 months (risk difference, 0.00; 95% CI, -0.02 to 0.01) (moderate SOE for no difference).
- Evidence was insufficient to draw conclusions about use of health care services. Hospitalizations were reported in two trials. In one of post-CABG patients at 8 months, overall, 33 percent of intervention patients, 32 percent of controls, and 25 percent of a nondepressed comparison group required hospitalization. In a trial of diabetic patients with or without heart disease, 27 intervention patients versus 23 controls were hospitalized at 12 months.
- Patients receiving the collaborative care intervention generally experienced greater quality of life than control patients at 6 and 12 months, based on several different measures (moderate SOE).
- Six trials, using various methods, reported costs of the intervention. Of the four studies that reported it similarly, the average cost of the intervention was \$542.00 annually per patient.

Detailed Synthesis

Morbidity Related to Chronic Medical Condition

The IMPACT arthritis subgroup reported on daily pain interference, using a scale ranging from 0=no interference to 10=unable to perform any activities.^{60, 63} Intervention patients had significantly less pain interference than control patients at 6 months (4.08 vs. 4.65; between-group difference -0.56; 95% CI, -0.96 to -0.16) and 12 months (4.40 vs. 4.99; between-group difference -0.59; 95% CI, -1.00 to -0.19).

The Bypassing the Blues study used a heart disease-specific measure of physical functioning, the Duke Activity Status Index (DASI);⁸³ in this, a change of 3 or more points has been considered the minimal clinically important difference.^{83, 84} The investigators reported that patients in the collaborative care group had better scores on this measure than controls at 8 months (between-group difference 4.6; 95% CI, 1.9 to 7.3; $p=0.001$);⁷⁴ both arms of the trial showed an overall improvement over time. Analyses by sex showed that the significantly better scores among intervention patients were found only among males (between-group difference for men, 6.1; 95% CI, 2.7 to 9.6; $p<0.001$; for women, 3.1; 95% CI, -1.1 to 7.3).

The Rollman et al. study of post-CABG patients also examined hospitalizations for cardiovascular causes (intervention=85 vs. control=68).⁷⁴ Total hospitalizations are reported under health care utilization and in Appendix C.

Mortality

All-cause mortality was reported in eight studies (Appendix C). Unsurprisingly, it was higher among cancer patients than those with other chronic conditions. In one small (N=55) 8-month study of cancer patients,⁶⁴ no deaths occurred in the intervention arm, and eight patients (30 percent) in the control arm died (OR 0.04; 95% CI, 0.002 to 0.74). In the other two studies of cancer patients,^{59, 66} mortality was similar across treatment arms at all time points.

In our meta-analyses, we detected no difference in mortality between groups at 6 months or 12 months (Table 15), with few events overall. The Pathways study⁷⁰ reported deaths at 5 years (intervention=10.3 percent vs. control=12.8 percent); these data were not included in the pooled analyses.

Use of Health Care Services

Two studies reported hospitalizations. We reported cardiac-related rehospitalization in the study of post-CABG patients⁷⁴ under condition-specific morbidity as noted above. That same study gave the total number of hospitalization in 8 months; overall, 33 percent of intervention patients, 32 percent of controls, and 25 percent of a nondepressed comparison group, required hospitalization. The TEAMcare trial (patients with diabetes and/or heart disease) reported that 27 (25.5 percent) of intervention patients and 23 control patients (21.3 percent) were hospitalized at some point during the previous 12 months.

We found no other reports of health care utilization.

Table 15. Summary of meta-analyses for general health outcomes

Outcome	Timing	N Studies	Statistic	Effect Size	95% CI	I ²
All cause mortality	6 months	7	RD	0.00	-0.02 to 0.02	62.9
All cause mortality	12 months	7	RD	0.00	-0.02 to 0.01	0.00
Self-rated physical health	6 months	4	SMD	0.19	0.08 to 0.31	0.00
Self-rated physical health	6 months	3	WMD	2.12	0.75 to 3.49	0.00
Self-rated physical health	12 months	3	WMD	1.25	-0.45 to 2.95	27.21

Abbreviations: CI, confidence interval; RD, risk difference; SMD, standardized mean difference; WMD, weighted mean difference.

Physical Health Quality of Life

Five studies^{62, 65, 66, 68, 74} measured self-reported quality of life using the physical component of SF-12^{62, 65, 66, 68} or 36 (SF-36).⁷⁴ We conducted meta-analyses for these outcomes, using WMD where measures were similar (all SF-12), and SMD to include the trial using the SF-36, at 6 and 12 months (Table 15). Our findings show that patients in the collaborative care groups had higher self-rated physical health status than controls at 6 months. At 12 months the WMD did not show a difference between groups (1.25; 95% CI -0.45 to 2.95). For context, 3 points is suggested as the minimally important clinical difference on the SF-36.⁸⁵

Similar to the more condition-specific DASI reported under morbidity outcomes above, the post-CABG study showed no between-group difference overall at 8 months on the SF-36 (1.6; 95% CI, -0.5 to 3.8).⁷⁴ When the analyses were done by sex, men in the intervention group had significantly higher scores than men in the control group (3.6; 95% CI, 0.8 to 6.3).

The HIV study also collected the Quality of Well-Being Self-Administered Scale (QWB-SA), which ranges from death (0.0) to perfect health (1.0); the investigators reported no between-group differences at 6 months (-.03; 95% CI, -0.01 to 0.06) or 12 months (-0.01; 95% CI, -0.05 to 0.03).⁶⁸

Williams et al., in their diabetic sample,⁶² used a self-rated measure of health-related functioning (0=no problem to 10=unable to function). They showed that intervention subjects reported significantly better functioning than controls at 6 months (4.37 vs. 4.63) and 12 months (3.91 vs. 4.90).

The arthritis subgroup analysis from IMPACT reported self-rated general health status on a scale ranging from 1 (excellent) to 5 (poor).^{60, 63} The investigators showed that intervention participants gave a significantly better rating than controls at 12 months (3.3 vs. 3.6, $p < 0.001$). The same study also asked participants to rate their overall quality of life in the past month on a scale of 0 to 10 (zero=your situation is about as bad as dying); this measure also favored the intervention group at 12 months (6.4 vs. 6.0, $p = 0.005$). The same scale was reported in the IMPACT cancer cohort;⁵⁹ intervention subjects gave better scores than controls at 12 months (6.7 vs. 6.0, $p = 0.04$) but not 6 months (6.3 vs. 5.7, $p = 0.86$).

Despite negative results in the HIV study, the general trends (including meta-analysis at 6 months with HIV included) across studies and measures suggest that patients receiving the collaborative care intervention experienced greater quality of life than control patients at both 6 and 12 months.

Costs of Intervention

Table 16 details costs of interventions in the trials that reported them. In some cases, the costs are per person or per service; in others, they are combined or total costs. Some investigators reported intervention (total) costs over a specified time period; others did not. No trial compared costs for collaborative care with those for usual care.

Table 16. Costs of interventions

Author, Year Study Name Chronic Condition Quality	Costs
Ell et al. 2008 ⁶⁶ ADAPt-C Cancer Fair	\$524 per intervention patient over 12 months ^a
Strong et al., 2008 ⁶⁹ SMaRT Oncology 1 Cancer Fair	\$523 per patient over the 6-month intervention period ^b
Ell et al., 2010 ⁶⁵ MDDP Diabetes Fair	\$820 per patient over the 12-month intervention period ^c
Katon et al., 2008; ⁷⁰ Pathways Diabetes Fair	\$543 per patient from baseline through 12 months ^d
Katon et al., 2006 ⁶¹ IMPACT (secondary analyses) Diabetes Fair	\$597 per patient over 24 months ^e
Katon et al., 2010 ⁷⁵ TEAMcare Diabetes and/or heart disease Fair	\$1,224 per patient over the 12-month intervention period ^f

^a Inclusive of costs for intervention provider and patient navigation services, telephone and in-person supervision, evaluation and prescription by study psychiatrist, and intervention materials.

^b Direct cost of nurse time + psychiatrist time, exclusive of nurse training and screening time.

^c Assumptions: \$71 per 90-minute visit, \$35 per 45-minute telephone follow-up, \$10 per 10- to 15-minute patient navigation call, \$10 for relaxation tape, \$136 for interventionist communication with PCP, \$21 for clinical supervision.

^d Unspecified “intervention visit” costs; assumptions: \$79 per 30-minute in-person nurse visit, \$31 for each 10- to 15-minute telephone contact, \$57 for supervision and information system support.

^e Inclusive of in-person and telephone contacts, overhead costs, supervision, and intervention materials.

^f Inclusive of nurse contacts, physician supervision, and information systems support; mean of 10.0 in-person and 10.8 telephone visits; assumptions: \$79 per 30-minute in-person nurse visit, \$31 per 10- to 15-minute telephone nurse contact, \$100 fixed costs per patient for supervision and information systems support.

Abbreviations: ADAPt-C, Alleviating Depression Among Patients with Cancer; CI, confidence interval; IMPACT, Improving Mood—Promoting Access to Collaborative Treatment; SD, standard deviation; SMaRT, Symptom Management Research Trials.

Applicability

We refer to the applicability section in KQ 1a for the same consideration of constraints posed by these types of studies, specifically the required presence of a care manager to carry out the intervention. In general, the results in this section apply to a primary care population with depression and one of the chronic medical conditions discussed here. Some data were available on outcomes for patients with arthritis, cancer, diabetes, heart disease, and HIV, but they were too sparse to generalize to the population level based on condition. These studies did, however,

include patients with significant medical morbidity, and as such they reflect real-world circumstances.

Key Question 3: Harms of collaborative care interventions

All the studies that met our eligibility criteria characterized their intervention as a form of collaborative care. We examined the body of evidence for any reported adverse events (AEs), but we recognized that potential harms reported as a direct effect of this type of intervention are rare.

Key Points

- Very few data on harms were reported.
- The trial that specifically reported AEs, such as medication side effects or emergency room visits for chest pain or neurologic symptoms, found overall rates to be higher among intervention patients than controls.
- More frequent medication adjustments and monitoring of self-reported patient outcomes in the collaborative care arm may have contributed to the higher reported rate of AEs in that single trial.

Detailed Synthesis

We reported deaths and hospitalizations in KQs 1 and 2. One trial, in patients with depression and diabetes and/or heart disease,⁷⁵ considered the following to be mild and moderate AEs: falls, medication side effects, extremely high laboratory values, and emergency room visits for chest pain or neurologic symptoms. Mild and moderate AEs were self-reported, and the severity was based on a study clinician's judgment. Two patients (1.9 percent) in the collaborative care arm experienced at least one mild AE; no patient in the control arm had any mild AE. At least one moderate AE was experienced by 17 percent of intervention patients and 3 percent of control patients.

The higher rate of mild and moderate AEs in the intervention arm may be attributable to increased rates of medication adjustment rather than the overall collaborative care intervention itself. Additionally, patients in the intervention arm had more frequent contacts with the interventionist and, therefore, had more opportunities to report adverse events.

Applicability

Given the factors related to applicability noted in KQs 1 and 2, these results must be considered in the context of heterogeneity across medical conditions and interventions. Collaborative care is a complex intervention, and harms of the intervention itself may be difficult to assess. These results may also not apply to patients with fewer symptoms of depression.

Key Question 4: Characteristics of service-level interventions

This question was addressed in the context of studies that met criteria for KQs 1 and 2. The populations for the included studies all identified depression as the mental health condition. All interventions were described as collaborative care interventions; we found no studies with other types of practice-based interventions meeting our inclusion/exclusion criteria. The purpose of this key question is to compare and contrast characteristics of the collaborative care intervention.

Key Points

- Components of the Intervention
 - Team Composition. Care teams were diverse and included various combinations of nurses (6 studies), psychologists or counselors (3 studies), social workers (3 studies), supervising psychiatrists (10 studies), independent physicians (4 studies), and a pharmacist (1 study).
 - Main Intervention Provider. The collaborative care intervention was typically delivered by a care manager alone or in concert with another member of the research team. In most cases the care manager was a nurse (six studies), a master's or doctoral-level psychologist or counselor (two studies), or a social worker (three studies); most had received formal depression care training that focused on diagnosis, pharmacotherapy, and problem-solving treatment.
 - Approach and Mode of Delivery. Across studies, the collaborative care intervention incorporated some degree of personalized care, usually in the early stages of the intervention, along with some combination of telephone alone or telephone plus face-to-face sessions. Care often was implemented using a stepped approach, allowing for patient preferences and following established guidelines.
 - Self-management. The collaborative care intervention typically featured some degree of self-management education and monitoring.
- Intensity of the Intervention
 - Session Frequency. After an initial information and education session, care providers talked with or met participants face-to-face for multiple sessions across a period of time ranging from weeks to months. The number of sessions depended sometimes on the study design and sometimes on the pace at which the individual patient responded to treatment. Two studies were solely telephone based.
 - Session Duration. Across studies that reported session duration, the initial information/education session was typically longer than follow-up sessions. The latter varied in length from 5 to 45 minutes.

Detailed Synthesis

Ten studies were available to address this key question.^{37, 39, 59-75} Components of the interventions that differed across studies included the composition of the treatment team members, type of provider who delivered the intervention, mode of delivery of the intervention, and the intensity (frequency and duration) of treatment sessions. All studies had in common some degree of personalizing the intervention for the individual patient and use of a stepped care approach, although the specific nature of the stepped care approach differed in complexity and evidence base across studies.

Also common across studies were other core components, many of which were based on the model of the IMPACT trial. These components included (1) a depression care specialist or manager who was typically responsible for patient education, brief problem-solving counseling, symptom monitoring, and follow-up telephone calls to facilitate relapse prevention; (2) a consulting psychiatrist on the collaborative care team who supervised the care manager and communicated directly with primary care providers of patients who did not respond adequately to treatment; and (3) use of a validated instrument to document change in depressive symptoms

over the course of treatment. We could not develop any summary statistics relevant to this question or grade strength of evidence.

Some similarities as well as differences emerged across studies in terms of how and by whom the intervention was delivered (Table 17). In *Bypassing the Blues*,⁷⁴ *HITIDES*,⁶⁸ *Pathways*,^{37, 39, 70-73} *SMaRT Oncology 1*,⁶⁹ and *TEAMcare*,⁷⁵ the collaborative care intervention was delivered by a nurse, who was described as being part of the research staff with the exception of one study in which the nurse's relation to the study team was unclear.⁶⁹ In the remaining studies, the intervention was delivered by a trained counselor;⁶⁷ a social worker;⁶⁴⁻⁶⁶ or, using a hybrid approach (*IMPACT*), either a nurse or psychologist.⁵⁹⁻⁶³ In the majority of studies the nurse,^{37, 39, 68, 70-73} social worker,^{64, 65} or psychologist^{59-61, 63} was a formally trained depression care specialist.

The individual responsible for providing direct patient management (e.g., the depression care specialist) was part of a larger care team. This team included a psychiatrist in all studies, as well as another physician in some trials.^{37, 39, 59-63, 70-75} One trial was unique in including a pharmacist as part of the supervisory team.⁶⁸

All trials provided some degree of personalized care, usually during the initial stages of treatment planning; all typically had a structure that included multiple contacts between the care team provider and the patient. Early in treatment, the intervention was personalized by allowing the patient some degree of autonomy in selecting to begin treatment with medication, psychotherapy, or both. Thereafter, treatment recommendations were adjusted according to a patient's symptom response, including increasing the medication dose or contact with the care provider (or both). Two trials relied solely on telephone contact to deliver the intervention;^{68, 74} the others used some combination of weekly,⁶⁴ twice per month,^{37, 39, 68, 70-75} or variable frequency^{59-63, 65-67, 69} face-to-face sessions and follow-up telephone calls. The *Pathways*^{37, 39, 70, 71, 73} and *IMPACT*⁵⁹⁻⁶³ trials described the initial information and education session as lasting 1 hour, whereas other studies were less descriptive. Session length varied from 5 minutes^{59-61, 63} to 30 minutes^{37, 39, 70, 71, 73} to 45 minutes^{59-61, 63, 69} or was unspecified.^{64, 66-68, 74, 75}

The actual number of treatment sessions differed considerably across trials. In one case it was capped at 10.⁶⁹ In the others, it varied over a predetermined length of followup according to the patients' needs (i.e., if response to treatment was unsatisfactory, more frequent follow-up sessions were allowed).^{37, 39, 59-61, 63, 66, 70, 71, 73-75}

Self-management training and reinforcement were integral to the collaborative care interventions. For example, patients received advice and skill-building opportunities regarding sleep hygiene, appropriate levels of physical activity or other pleasant life events, healthy nutrition, and tobacco and alcohol use;^{37, 39, 70, 71, 73, 74} scheduling pleasant life events;⁵⁹⁻⁶³ coping behaviors;⁶⁹ and medication adherence.⁷⁵ In some instances, these behaviors and activities were tracked during the trial and included as study outcomes.

Table 17. Summary of service-level characteristics of included studies

	ADAPt-C ⁶⁶	Bypassing the Blues ⁷⁴	HITIDES ⁶⁸	IMPACT ⁵⁹⁻⁶³	MDDP ⁶⁵	MODP ⁶⁴	Pathways ^{37, 39, 70-73}	SMaRT Oncology 1 ⁶⁹	TEAMcare ⁷⁵	Vera et al. ⁶⁷
Care provider										
Nurse		X	X	X			X	X	X	
Psychologist/counselor				X					X	X
Social worker	X				X	X				
Supervisory team										
Psychiatrist	X	X	X	X	X	X	X	X		X
Physician		X		X			X		X	
Pharmacist			X							
Stepped approach										
IMPACT algorithm				X						
Modified IMPACT	X				X	X	X			
Other		X	X						X	X
None								X		
Self-management										
Pleasant life events	X	X	X	X			X			
Healthy lifestyle		X	X		X		X			
Coping					X			X		
Medication/treatment adherence	X				X	X			X	

Abbreviations: ADAPt-C, Alleviating Depression Among Patients with Cancer; HITIDES, HIV Implementation of Translating Initiatives for Depression into Effective Solutions; IMPACT, Improving Mood—Promoting Access to Collaborative Treatment; MDDP, Multifaceted Diabetes and Depression Program; MODP, Multifaceted Oncology Depression Program; N/A, not applicable; SMaRT, Symptom Management Research Trials.

Applicability

The majority of trials hired research staff, many with special training in depression or diabetes care, to work directly with patients. For that reason, these findings may not generalize to settings that do not have (or cannot afford) a care manager. This limitation may be most relevant to community health centers and departments and small specialty practices (e.g., obstetrics and gynecology). This collection of trials focused on five major concomitant medical conditions: arthritis, cancer, diabetes, heart disease, and HIV. Missing from this literature are studies that focused on patients with chronic pulmonary disease, chronic pain, or stroke or on the frail elderly. Four trials focused almost exclusively on Hispanic or Latino participants,⁶⁴⁻⁶⁷ whereas other trials had percentages of minority participants that were reflective of their presence in the general U.S. population.^{37, 39, 59-63, 68, 70, 71, 73, 75} No studies, however, were designed *a priori* to evaluate racial or ethnic differences in outcomes or in acceptability of, or barriers to, treatment. Thus, specific applicability to racial or ethnic subgroups is unclear.

Key Question 5: Characteristics of the practice setting

Key Points

- Overall, practice setting characteristics (e.g., geographic location, practice type and size, open/closed system, level of integration, payer mix and payer type, service mix, information technology) and system characteristics (e.g., financing of care and payment arrangements) were rarely reported.
- Nine trials were conducted in the United States (one in Puerto Rico) and one in the United Kingdom (Scotland).
- None of the trials explicitly reported on whether it was conducted in an open (no membership or eligibility required) or closed system, although the IMPACT trial⁵⁹⁻⁶³ was conducted in a mix of systems that included primary care clinics in a large health maintenance organization (HMO) as well as the Department of Veterans Affairs (VA) system. Three studies were presumed to be conducted in closed systems.^{37, 39, 68, 70-73, 75} Closed systems included Group Health Cooperative and the VA system.

Detailed Synthesis

Characteristics of the Practice Setting

Geographic Location

Nine trials were conducted in the United States (one in Puerto Rico);^{37, 39, 59-68, 70-75} one trial was conducted in the United Kingdom.⁶⁹

No trial explicitly reported whether the practice setting was urban, rural, or mixed. Three could be presumed to be urban based on information provided in the articles,⁶⁴⁻⁶⁶ and one could be presumed as mixed setting based on information provided by authors.⁶⁷ The IMPACT trial subgroup analyses⁵⁹⁻⁶³ were presumed to be mixed setting based on information provided in an article by Unutzer and colleagues.⁵ For the remaining four trials, rural versus urban setting was not noted clearly nor could be inferred based on information in the articles.^{37, 39, 65, 68-73, 75} One trial was telephone delivered;⁷⁴ hence, urban or rural setting was not deemed relevant for reporting.

Practice Type and Size

Nine of the 10 trials were conducted in primary care or primary care–like settings. Intervention in 1 trial was conducted by telephone.⁷⁴

The majority of trials did not report practice size, and, when they did, the reporting was inconsistent. One trial was conducted in a cancer center that served 1.5 million people.⁶⁹ Another trial reported HMO size (500,000) and number of patients (9,063) that met case identification based on the HMO’s population-based diabetes registry, but it did not mention practice size.^{37, 39, 70-73}

Open Versus Closed System

System was categorized as open (no membership or eligibility required) in six trials,^{64-67, 69, 74} and three were perceived to be closed.^{37, 39, 68, 70-73, 75} Closed systems were generally self-contained; in this evidence base, they included Group Health Cooperative and the VA system, where an array of services was accessible to patients who were members of these organizations. The IMPACT trial subgroup analyses⁵⁹⁻⁶³ enrolled patients from a mix of settings, including some perceived as closed, such as a large HMO.⁵ None of the trials explicitly reported on this variable.

Level of Integration: Presence of Mental Health Services On-Site

We defined the level of integration by whether mental health services were available on-site (see Appendix C for trial-specific data), because these trials did not give other descriptors of integration. On-site mental health providers in primary care clinics were described in four trials.^{37, 39, 64, 66, 69-73} One trial reported that part-time registered nurses with experience in diabetes education collaborated with primary care providers to implement the intervention.⁷⁵ One trial reported that mental health providers for primary care–like settings were located off-site,⁶⁸ and another noted that the study team—including care managers, mental health specialist, and psychiatrist—was separate from the primary care practice.⁶⁷ For the IMPACT trial subgroup analyses,^{5, 59-63} we could infer that depression care managers (nurses) were physically present in three primary care clinics; in another three clinics, some mental health care practitioner was available on-site whereas in the rest of 12 clinics, none were present on-site. Two trials did not report any information regarding the location of mental health services.^{65, 74}

Payer Mix and Payer Type

We defined payer mix as the type of insurance plan. Payer mix or type was not reported for four trials.^{64, 66, 67, 74} Two trials described participants as members of Group Health Cooperative, a mixed-model prepaid health plan.^{37, 39, 70-73, 75} One group reported that participants were either enrolled in Medicaid/Medicare, a county-funded program, or had no health insurance.⁶⁵ In one trial, all participants were covered by VA benefits.⁶⁸ For the IMPACT trial subgroup,⁵⁹⁻⁶³ based on information provided in an article by Unutzer and colleagues,⁵ a considerable majority of patients had Medicare coverage (77 percent) and prescription drug coverage (90 percent). This trial was conducted in 18 primary care clinics, which included patients from 9 HMO/Independent Provider Association practices, 3 VA practices, 5 academic group-practice practices, and 1 private group practice.

Service Mix

Service mix referred to the types of services available at each intervention site. No trial reported service mix.

Information Technology

We defined information technology (IT) to include electronic medical records (EMRs) and how well they were integrated for the intervention and decision support. Decision support included computer-based prompts and/or algorithm triggers related to the disease of interest used as part of the intervention.

These trials gave only limited descriptions of whether and how they used information technology. Half of the trials did not mention health IT or EMRs.^{64-67, 69} Another four trials mentioned health IT or EMR,^{37, 39, 59-63, 68, 70-73, 75} but two of these did not describe in detail the specific IT features that the intervention employed. See Appendix C for trial-specific details on use of information technology for concomitant care interventions in these four trials. Finally, although one trial⁷⁴ did not report use of IT system or EMRs for delivery of concomitant care, it did report that data and safety monitoring was done electronically. The EMR was searched for an increase of 25 percent or more in a Hamilton Rating Scale for Depression (HRSD) score; this triggered a written letter to the treating physician and an offer to identify local mental health specialists and provide additional treatment advice.

Relationship Between Elements of the System in Which the Practice Operates

Financing of Care

Financing of care was not reported for six studies.^{37, 39, 59-63, 65, 68, 70-75} Two trials^{64, 67} reported that the study itself covered treatment costs, including medication and therapy. One trial reported that participants were reimbursed for time spent completing outcome interviews and for transportation and copays for antidepressant medications if applicable.⁶⁶ One trial reported that medical treatments for patients were financed through the U.K. (Scotland) National Health Service.⁶⁹

Payment Arrangements

Payment arrangements include financial arrangements between primary care providers and mental health providers and may include financial resource sharing or incentives. No trial described payment arrangements.

Applicability

These findings generally apply to patients with depression and one or more medical conditions who are receiving care in settings that provide care management. Most trials occurred in the United States, so findings cannot be extended to other countries in general. Even though the systems of care were not well characterized, they likely differed considerably. How such infrastructure influences the delivery of collaborative care is not clear from our findings, and results should be considered with that in mind.

Discussion

In this report, we aimed to address the following overarching question: Among adults with chronic medical conditions and concomitant mental health condition (such as patients with diabetes and depression) treated in the primary care setting, what is the comparative effectiveness of practice-based interventions aimed at improving the mental health condition or both the mental health and chronic medical conditions?

We broadly defined the scope of our review to include real-world scenarios and patients with clear diagnoses, representing common primary care populations. However, although studies we identified involved several coexisting medical conditions, included studies involved only a single mental health condition, depression. The variety of interventions was similarly limited. Indeed, despite an effort informed by our Technical Expert Panel to be inclusive of practice-based interventions (such as integrated care or telemedicine), the studies in our final analysis all defined their intervention as a form of collaborative care. No study compared its intervention with another intervention; rather, all did comparisons only with usual or enhanced usual care. Therefore, this discussion is based on a body of evidence comparing the effectiveness of collaborative care interventions with usual care for primary care patients with depression and one or more chronic medical conditions, and does not include any head-to-head trials.

Searching for a broad range of chronic medical conditions that the Agency for Healthcare Research and Quality (AHRQ) and the Institute of Medicine (IOM) have identified as being of high priority for research, we identified studies on arthritis, cancer, diabetes, heart disease, HIV, and one or more conditions. Nine studies were primary randomized controlled trials (RCTs); five articles were from condition-specific subgroup analyses of a separate RCT (representing the 10th trial), with the most data available on patients with diabetes. All trials except one were designed to measure mental health–related outcomes, rather than medical outcomes, as the primary outcome.

Our review focuses on five main groups of outcomes: mental health outcomes (KQ 1), chronic disease medical outcomes (KQ 2), harms of interventions (KQ 3), components of interventions (KQ 4), and characteristics of practice settings in which the interventions occurred (KQ 5).

Key Findings and Strength of Evidence

Key Question 1a: Intermediate Mental Health Outcomes and Satisfaction With Care

We summarize findings and strength of evidence (SOE) for this question in Table 18. Evidence from eight RCTs and two subgroup analyses indicated that patients receiving a collaborative care intervention had greater improvement in depressive symptoms and in depression treatment response (≥ 50 percent reduction in symptoms) than those receiving usual care (moderate SOE). These results were consistent across medical conditions and reflect clinically meaningful changes on well-accepted measures of depression. The evidence showed that five patients would need to be treated to achieve one more depression response than would be seen with usual care at 6 months, with a number needed to treat [NNT] of six patients at 12 months.

Table 18. Summary of results for collaborative care interventions compared with controls for people with depression and one or more chronic medical conditions: intermediate mental health outcomes

Outcome	Summary of Results	Strength of Evidence
Symptom improvement	Greater symptom improvement scores in intervention groups at both 6 months (SMD, 0.45; 95% CI, 0.29 to 0.61) and 12 months (SMD, 0.47; 95% CI, 0.29 to 0.65) compared with control groups (10 studies).	Moderate
Depression-free days	More depression-free days at 12 months for those in intervention groups than usual care groups (4 studies, range of differences between intervention and control groups: 17 to 54 days)	Moderate
Response ($\geq 50\%$ reduction)	Higher rates of depression response in intervention groups than usual care, based on 8 RCTs and 2 RCT subgroup analyses (NNT, 5 at 6 months; NNT, 6 at 12 months)	Moderate
Remission	Remission of depression favored intervention over usual care at 6 months and at 12 months based on 3 RCTs and 2 RCT subgroup analyses (NNT, 8 at 6 months; NNT, 12.5 at 12 months)	Moderate
Recurrence	No studies addressed recurrence of depression	Insufficient
Treatment adherence	Mixed results: 1 trial reported significantly greater adherence to antidepressants in the intervention arm at 6 and 12 months; the other reported no difference between groups at 6 and 12 months.	Insufficient
Treatment satisfaction	Greater satisfaction with care for intervention participants than controls RD, 0.21 (95% CI, 0.11 to 0.30) ^a	Moderate

^a Results are from meta-analysis of the 4 trials that reported satisfaction for both intervention and control arms. Two additional trials reported treatment satisfaction for the intervention arm but not the usual care arm.

Abbreviations: CI, confidence interval; NA, not applicable; RD, risk difference; SMD, standardized mean difference; WMD, weighted mean difference.

Although less frequently measured, patients receiving collaborative care also had more depression-free days (moderate SOE) and higher rates of depression remission (moderate SOE) compared with patients receiving usual care. Intervention patients similarly reported greater satisfaction with care (moderate SOE).

Evidence was insufficient (based on limited data) to draw conclusions about adherence to antidepressants (conflicting evidence) or about recurrence of depression (no trial).

Key Question 1b: Morbidity, Mortality, Quality of Life, Function, and Utilization

This question looked at other mental health outcomes, including suicide, use of antidepressants, mental health–related quality of life, use of mental health care services, sick days related to mental health, and employment stability (Table 19). Only one suicide was reported, in the usual care arm of a cancer trial.⁶⁹ Based on data from three studies at 6 months and five studies at 12 months, use of antidepressants was greater in collaborative care arms than in control groups across populations with various chronic medical conditions (low SOE). Quality of life was measured in several ways but most frequently using the mental component of the Medical Outcomes Study Short-Form (SF-12), showing that collaborative care interventions achieved greater quality of life scores than usual care at 6 and 12 months (moderate SOE). Four studies reported on health care utilization; each showed greater use of any mental health services at 6 or 12 months (or both) by those receiving the collaborative care intervention (low SOE). No data were available on sick days or employment stability (insufficient).

Table 19. Summary of results for collaborative care interventions compared with controls for people with depression and one or more chronic medical conditions: other mental health outcomes

Outcome	Summary of Results	Strength of Evidence
Suicide	One study reported one suicide in the usual care group.	Insufficient
Use of anti-depressants	Greater antidepressant use for collaborative care interventions than for usual care at 6 and 12 months (RD, 0.22; 95% CI, 0.13 to 0.32 at 12 months)	Low
MH-related quality of life	Greater mental-health-related quality of life for subjects in collaborative care intervention arms than usual care at 6 and 12 months using the mental component of the Medical Outcomes Study Short Form (WMD, 2.98; 95% CI, 1.41 to 4.56 at 12 months)	Moderate
MH care utilization	Greater use of any mental health services for collaborative care interventions than for usual care at 6 and/or 12 months (42% to 97% vs. 16% to 57% for intervention and control groups, respectively; based on 4 studies)	Low
MH-related sick days	Not reported	Insufficient
MH-related employment stability	Not reported	Insufficient

^a Results of the meta-analysis excluding the HITIDES data

Abbreviations: CI, confidence interval; HITIDES, HIV Implementation of Translating Initiatives for Depression; MH, mental health; mths, months; NA, not applicable; RD, risk difference; SMD, standardized mean difference; WMD, weighted mean difference.

Key Question 2a: Intermediate Chronic Medical Outcomes

For this question, we were interested in the effects of collaborative care interventions on intermediate outcomes for the specified chronic medical condition(s). For most chronic medical conditions of interest here, we found just one study (Table 20). We found multiple studies of people with diabetes and depression.

Hemoglobin A1c (HbA1c) was reported as a measure of response in four trials of people with diabetes; baseline HbA1c ranged from 7.28 percent to 9.03 percent. Our meta-analyses found no significant differences between intervention and control groups (WMD, 0.13; 95% CI -0.55 to 0.41 at 6 months; WMD, 0.24; 95% CI, -0.14 to 0.62 at 12 months) (low SOE). However, the only study to use HbA1c as a predefined outcome measure, the TEAMcare study,⁷⁵ reported significant differences in HbA1c. The figures were as follows for intervention versus control groups: 8.14 versus 8.04 at baseline; 7.42 versus 7.87 at 6 months; and 7.33 versus 7.81 at 12 months (overall $p < 0.001$).

Three studies reported on adherence to recommended treatment.^{62, 72, 75} The subjects in the collaborative care intervention were no more likely than controls to adhere to a generally healthy diet (moderate SOE), but they were more likely to adhere to an exercise program in two of three studies (low SOE). For rates of adherence to an overall regimen (including oral hypoglycemics, lipid-lowering agents, and angiotensin-converting enzyme inhibitors), evidence was insufficient to draw conclusions.

Data were insufficient to draw conclusions about treatment satisfaction.

Table 20. Summary of results for collaborative care interventions compared with controls for people with depression and one or more chronic medical conditions: intermediate chronic medical outcomes

Outcome	Summary of Results	Strength of Evidence
Symptom improvement		
Arthritis: pain	Insufficient evidence from 1 subgroup analysis to draw conclusions	Insufficient
HIV: symptom severity	Insufficient evidence from 1 RCT to draw conclusions	Insufficient
Response		
Diabetes: HbA1c	3 RCTs and 1 subgroup analysis showed no between-group differences at 6 or 12 months.	Low
Heart disease: ≥ 10 mmHg decrease in SBP	Insufficient evidence from 1 RCT to draw conclusions	Insufficient
Adherence		
Cancer: followed treatment	Insufficient evidence from 1 RCT to draw conclusions	Insufficient
Diabetes: diet	Not calculated; no between-group difference at any time points in all studies examined	Moderate
Diabetes: exercise	2 trials favored intervention; 1 trial found no difference	Low
Diabetes: medications	Insufficient evidence from 2 studies (1 RCT, and 1 subgroup analysis) to draw conclusions	Insufficient
HIV: medications	Insufficient evidence from 1 RCT to draw conclusions	Insufficient
Satisfaction with care		
Diabetes, heart disease, or both	Insufficient evidence from 1 RCT to draw conclusions	Insufficient

Abbreviations: CI, confidence interval; mmHg, millimeters of mercury; OR, odds ratio; RCT, randomized controlled trial; SBP, systolic blood pressure; WMD, weighted mean difference.

Key Question 2b: General Health Outcomes and Costs

General health outcomes of interest included condition-specific morbidity, mortality, health care utilization, and quality of life. All evidence was insufficient to draw conclusions other than for mortality and quality of life (Table 21).

Eight studies reported on mortality and few deaths were reported overall. Most were in studies of people with cancer. Intervention and control subjects did not differ in mortality at 6 months (risk difference [RD], 0.00; 95% CI, -0.02 to 0.02) or 12 months (RD, 0.00; 95% CI, -0.02 to 0.01) (moderate SOE). Patients receiving collaborative care interventions generally experienced greater quality of life than control patients at 6 and 12 months, based on several different measures from six studies (moderate SOE).

Table 21. Strength of evidence for collaborative care interventions for people with depression and one or more chronic medical conditions: KQ 2b, general health outcomes and costs

Outcome	Summary of Results	Strength of Evidence
Condition-specific morbidity (arthritis)	Insufficient evidence from 1 RCT (post-CABG) and 1 subgroup analysis to draw conclusions	Insufficient
Mortality	Eight studies reported no difference between groups, with few overall events; 6 months: RD, 0.00 (95% CI, -0.02 to 0.02); 12 months: RD, 0.00 (95% CI, -0.02 to 0.01)	Moderate
Health care utilization	Data were insufficient to draw conclusions about use of health care services	Insufficient
Quality of life	Greater quality of life for those receiving collaborative care at 6 and 12 months, based on several different measures	Moderate
Cost of intervention	Data were insufficient because of no comparator data; intervention costs were reported for the intervention arm in 6 studies, using varying methods	Insufficient

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; RCT, randomized controlled trial; RD, risk difference.

Key Question 3: Harms

Very few data were reported on harms, leaving insufficient evidence to draw conclusions. Only the TEAMcare study, in patients with depression, diabetes, and/or heart disease,⁷⁵ defined adverse events (AEs); the investigators reported higher rates of mild AEs (e.g., medication side effects) and of moderate AEs (e.g., falls) in the intervention arm. These could be attributable more to increased rates of medication adjustment than to the overall collaborative care intervention itself. Additionally, patients in the intervention arm had more frequent contacts with the care manager and thus had more opportunities to report adverse events, so findings might be the result of detection bias.

Key Question 4: Characteristics of Service Interventions

All interventions were described as collaborative care interventions; we found no study with any other types of practice-based interventions that met our inclusion/exclusion criteria.

The summary finding was that collaborative care hinged on the role of care manager, whose training and expertise varied widely. A physician (9 of 10 were psychiatrists) supervised care; a form of stepped care, patient preferences for treatment, and self-management were central to most interventions. Table 17 (in the Results chapter presentation above for KQ 4) shows the detailed comparisons.

The TEAMcare study was the most original in its design. Its investigators had a goal not just of reducing depression, but also controlling risk factors for various diseases simultaneously using a nurse to support guideline-concordant care.

Key Question 5: Characteristics of the Practice Setting

Given that characteristics of the practice setting often determine the feasibility of implementing interventions, we were interested in assessing similarities and differences. Nine of ten trials were conducted in the United States (one of those in Puerto Rico). Overall, practice setting characteristics (e.g., location, practice type and size, open/closed system, level of integration, payer mix and payer type, service mix, information technology) and system characteristics (e.g., financing of care and payment arrangements) were rarely reported. We categorized the system as open (no membership or eligibility required) in six trials^{64-67, 69, 74} and closed in three trials.^{37, 39, 68, 70-73, 75} Closed systems were generally self-contained; in this

evidence base, they included Group Health Cooperative and the VA system, where an array of services was accessible to patients who were members of these organizations. This latter factor may be important for applicability because of the nature of collaborative care and its focus on coordination, which is arguably easier in a closed than in an open system of care.

Findings in Relationship to What Is Already Known

Our findings reinforce the evidence for the effectiveness of collaborative care interventions for treating depression in primary care.⁸⁶ Moreover, they add a level of detail that had previously (to our knowledge) not been systematically reviewed. We selected trials that required the diagnosis of one or more chronic diseases (rather than generic primary care samples), and we reported on both the depression and the chronic medical outcomes. This review also extended the parameters of primary care to include settings in which certain patients with chronic disease receive the majority of their care. We found that recipients of collaborative care had significantly greater improvement in depression outcomes as compared with patients receiving usual care, for people with arthritis, cancer, diabetes, heart disease, and HIV.

Although the relationship between depression and chronic disease is established,^{29, 87, 88} to what extent successful treatment of depression improves chronic medical conditions remains uncertain. Our review shows that investigators are beginning to examine these outcomes, particularly in diabetes, although largely as secondary outcomes and with inconclusive data at present.

One study in the review, TEAMcare,⁷⁵ is an exception because it identified markers of disease risk for multiple conditions as primary outcomes. Using a guideline-based “treat-to-target” approach delivered by a medically trained nurse, these investigators targeted patients with poorly controlled diabetes, coronary artery disease, or both and coexisting depression; their aim was to reduce overall risk factors. This approach is a detour from the traditional model, where the focus is on collaborative care of depression, presumably in the hope that treating depression will improve overall health. Perhaps partly because of the benefits of having an integrated health care system, TEAMcare recipients showed clear improvements not only in depression, but also in reducing HbA1c and SBP to target goals.

Implementation, Dissemination, and Role of Decisionmakers

Despite evidence for the use of collaborative depression care in primary care settings, and a recommendation from the President’s New Freedom Commission on Mental Health,⁸⁹ uptake of such interventions has been poor. Although financial and system barriers have been identified,⁹⁰ reasons that decisionmakers have not advocated for the dissemination of collaborative depression care are still unclear.

This review adds further evidence supporting the effectiveness of such interventions. We show that patients with multiple and specific medical conditions can achieve improvement in depression (moderate SOE), satisfaction with care (moderate SOE), and mental and physical quality of life (moderate SOE); patients with diabetes can achieve greater adherence to some aspects of self-care (low SOE).

Stakeholders for improving the quality of primary care can apply the findings in this review from several perspectives. One way these data might be used and further disseminated is in measuring quality, for instance, to meet new standards for the Patient-Centered Medical Home.⁹¹

Applicability

Our findings are generally applicable to primary care patients with depression (we found no studies of anxiety) and at least one chronic medical condition, but they may not apply to patients with medical conditions not addressed in this report. The average age across studies was 59, an age group likely to have chronic disease. For that reason, we cannot speak directly to the relevance of these results also to young adults with chronic disease. People of Hispanic origin (predominantly female)⁶⁴⁻⁶⁶ and male veterans⁶⁸ were represented and appeared to respond similarly across outcomes, but there were too few data to analyze separately. Reported studies used clinically meaningful measures and had study durations (at least 6 months) that provided a real-world context.

Although these trials represented several settings, including primary care–like cancer and HIV clinics, they all had in common a care manager who directed the intervention. The intermediate mental health outcomes achieved might, therefore, apply only to settings that can accommodate and afford to provide such services. Similarly, practices that agreed to participate in these trials may reflect a selection bias based on culture and willingness to collaborate.

Limitations of the Comparative Effectiveness Review Process

Outlining the scope of this evidence review posed a challenge in regard to defining the interventions of interest. With input from our Key Informants and members of our Technical Expert Panel, we ultimately arrived at the term *practice-based* to differentiate from person-level interventions such as medications or stand-alone psychotherapies. We did not find the term *practice-based* in the literature, but we used other eligibility criteria and some known interventions to inform our searches. Even though we also added the terms *collaborative care*, *integrated care*, and *telemedicine* to guide our search, we may have missed interventions that are not indexed in these categories.

We also recognize that limiting the eligibility to trials of patients with clear medical diagnoses may have missed some potentially relevant work. One example is a recent RCT of a novel intervention for patients with anxiety conducted in the primary care setting;³⁶ the trial did not require a coexisting medical condition.

Limitations of the Evidence Base

Few relevant trials reported medical outcomes specifically. We also acknowledge significant heterogeneity among conditions (e.g., cancer is different from diabetes). Only 1 of our 10 studies⁷⁵ was designed to answer KQ 2a about intermediate medical outcomes. The remainder aimed to look at mental health outcomes in patients with different medical conditions.

We had no head-to-head trials in our report; this meant that we could make comparisons only with usual or enhanced usual care. Although patients with anxiety and one or more chronic medical disorders would have been of great interest, we did not find any studies that met our criteria. We had only one study from outside the United States, highlighting the lack of similar literature from other countries. Although we characterized the components of the interventions, we were unable to evaluate quantitatively the determinants of effectiveness (i.e., “active ingredients”⁴⁰).

Research Gaps

Depression Treatment and Outcomes of Chronic Disease

Depression can negatively affect general medical illness, but we do not know whether the effective treatment of depression in the primary care setting can alter the course of chronic disease. To determine the relative benefit of implementing such programs, we need more studies designed to measure the effectiveness of depression care on medical outcomes in depressed primary care patients with medical conditions.

A growing body of literature is emerging for diabetes and heart disease (although still few focused on medical outcomes). Other common conditions, such as chronic lung disease and pain syndromes, need investigation. Researchers should try to selectively recruit patients with common disease clusters, such as diabetes, hypertension, and obesity, concomitant with depression; this group may be particularly salient given the probable role of vascular disease in late-onset depression.^{92, 93}

More generally, the bidirectional aspect of depression and medical illness needs further exploration. For example, investigators could usefully explore whether effectively improving vascular risk factors reduces depression.

Anxiety

We found no eligible studies involving anxiety. Given the significant medical morbidity and health care utilization associated with anxiety in primary care,⁹⁴ this absence is striking. We need to test practice-based models of care targeted to this population. One reason for the lack of research to date on such patients may be that the steps of screening and diagnosis of anxiety disorders in the primary care setting are less mature than they are for depression. Nonetheless, the feasibility of this work has been shown.³⁶

Head-to-Head Trials

Head-to-head trials of practice-based interventions should be considered; these might include collaborative care versus mental health co-location, or another model of integrated care versus collaborative care. Given the desire to find the active ingredients of practice-based care,⁴⁰ we should test variations of existing efficacious models. Certain components of the collaborative care model may be more salient than others, and future studies that explicitly compare intervention components within the collaborative care model may help address this issue. For example, head-to-head comparisons of telephone-based versus face-to-face approaches might be useful. Examining session frequency and/or study intensity (i.e., frequency plus duration) as a predictor of outcome within these two approaches may also prove fruitful.

Exploring the extent to which mental health and physical health outcomes are related to the intervention provider's training is another important issue; that could entail determining whether, for instance, outcomes improve by having a depression care specialist deliver the intervention rather than a provider not trained in mental health.

Answering some of these basic design questions in ways that facilitate comparisons with true interventions, and not simply usual care, will ultimately facilitate translation and implementation of these approaches on a broader scale.

Conclusions

In primary care patients with depression and one or more specific chronic medical conditions, collaborative care interventions achieved improvement in depression symptoms, response, remission and depression-free days (moderate SOE); satisfaction with care (moderate SOE); and mental and physical quality of life (moderate SOE). These improvements were consistent across different common chronic medical conditions. Patients with diabetes receiving collaborative care had greater adherence to some aspects of self-care (low SOE), but no difference in HbA1c (low SOE). To determine the relative benefit of implementing collaborative care programs on overall health, we need more studies designed to measure the effectiveness of depression care on medical outcomes. Future investigations should explicitly compare variations of practice-based interventions in head-to-head trials to examine determinants of effectiveness.

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