

# Relationship between depression and medication adherence in cardiovascular disease: the perfect challenge for the integrated care team

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**Abstract:** Many individuals with cardiovascular disease (CVD) experience depression that is associated with poor health outcomes, which may be because of medication nonadherence. Several factors influence medication adherence and likely influence the relationship between depression and medication adherence in CVD patients. This comprehensive study reviews the existing literature on depression and medication adherence in CVD patients, addresses the methods of and problems with measuring medication adherence, and explains why the integrated care team is uniquely situated to improve the outcomes in depressed CVD patients. This paper also explores how the team can collaboratively target depressive symptoms and medication-taking behavior in routine clinical care. Finally, it suggests the limitations to the integrated care approach, identifies targets for future research, and discusses the implications for CVD patients and their families.

**Keywords:** cardiovascular disease, medication adherence, self-management, electronic monitoring, integrated care, collaborative care, compliance

## Introduction

Cardiovascular disease (CVD) is the leading cause of death for American adults, and 85.6 million individuals in the United States are estimated to have one or more types of CVD.<sup>1</sup> It is also the leading source for US health care expenditures. Much of this health care expense stems from rehospitalization, which frequently follows failure to properly self-manage one's CVD.<sup>1</sup> In addition, many individuals with CVD experience depression,<sup>2</sup> a condition that is associated with poorer outcomes in CVD patients.<sup>3</sup> Medication nonadherence may help explain why depressed CVD patients experience poor outcomes; both depressed and nondepressed CVD patients are at risk of poor medication adherence.<sup>4</sup>

## CVD and depression

There are strong associations between depressive symptoms and CVD. Estimates of depression in CVD vary depending on the specific disease processes and assessment method, but ~50% of patients experience major or minor depression at least once in the course of experiencing CVD.<sup>5</sup> In a study that examined individuals hospitalized for myocardial infarction (MI), ~20% met the criteria for a major depressive episode based on a structured interview, and 31.1% self-reported significant depressive symptoms.<sup>6</sup> Individuals with heart failure (HF) seem to display a slightly increased prevalence – over one third – particularly when screened through self-report measures.<sup>7,8</sup> Mechanisms

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for the relationship of depression in CVD are unknown but may include autonomic imbalance, hypercoagulability, endothelial and vascular effects in women, inflammation, and indirect causation from behavior and nonadherence.<sup>9</sup> Independent predictors of depressive symptoms assessed in the hospital and 1 year post-discharge after MI include pre-MI vital exhaustion, history of depressive disorder, history of MI, poor ejection fraction, longer hospital stay, living alone, poor exercise tolerance, and female gender.<sup>10</sup>

## Depression and hospitalization or rehospitalization

Across CVD patients, depression is associated with increased health service use – depression predicts repeated HF hospitalizations<sup>11,12</sup> and rehospitalization after acute MI.<sup>13</sup> For example, acute MI patients with depressive symptoms experienced more emergency department visits and hospitalizations, were hospitalized sooner, and were hospitalized longer than acute MI patients without depression.<sup>13,14</sup> Similarly, the Heart Failure Adherence and Retention Trial examined whether an intervention of self-management skills and HF-specific education reduced a patient's likelihood of future hospitalizations.<sup>11</sup> Although the intervention had no effect on the primary endpoint of death or hospitalization for HF compared to HF-specific education alone,<sup>15</sup> depressed individuals demonstrated 1.45 times more HF-related hospitalizations than nondepressed patients even after adjusting for physician adherence to evidence-based medication use, patient adherence to HF medications and salt restriction, illness severity, HF severity, and socioeconomic factors.<sup>11</sup>

## Depression and mortality

The presence of depressive symptoms in patients with CVD predicts increased risk of death.<sup>3,16–18</sup> Major depression is associated with increased mortality 3 and 12 months following hospitalization for CVD<sup>19</sup> and 1 year after initial assessment in patients with HF.<sup>20</sup> However, despite decades of research, the scientific community does not fully understand the relationship between depression and mortality.<sup>21</sup>

Initiating treatment for depression through psychotherapy and pharmacotherapy does not eliminate the relationship between depression and mortality in CVD. In one study (Enhancing Recovery in Coronary Heart Disease Patients), researchers discovered that patients who experienced their first major post-MI depressive episode and individuals who experienced a recurrent episode upon MI both had significantly poorer survival rates than did nondepressed patients.<sup>22</sup> The researchers treated depression through cognitive

behavioral therapy (CBT) and a selective serotonin reuptake inhibitor (SSRI) when CBT alone did not significantly reduce depressive symptoms after 5 weeks.<sup>23</sup> Upon 5-year follow-up, individuals experiencing major or minor depression were at higher risk for all-cause mortality compared with individuals who were not depressed at follow-up.<sup>24</sup> Antidepressants do not eliminate the relationship between depressive symptoms and mortality in patients with HF.<sup>25</sup> Depression seems to affect the overall outcomes even when individuals seek treatment, suggesting that depression can powerfully influence the outcomes, and further studies are required to analyze the mechanism for this influence.

In another trial (the Sertraline Antidepressant Heart Attack Randomized Trial), researchers tested the safety and efficacy of sertraline in treating post-MI depression.<sup>26</sup> Sertraline seemed to work best in participants with a history of depression. Nevertheless, baseline depression severity and failure to improve depression substantially during treatment with either sertraline or placebo were strongly and independently associated with long-term mortality.<sup>26</sup> In additional studies, insufficiently treated depression and treatment-resistant depression following MI were associated with mortality after controlling for  $\beta$ -blocker use, sociodemographics, anxiety disorders, mortality factors, and health service utilization compared with treated patients.<sup>27</sup> Although previous research for decades has sought to improve the community's understanding of depression and consequently decrease mortality, the research findings to date are discouraging – this complex relationship seems to require a much more nuanced perspective.

In general, persistent depressive symptoms are associated with poor adherence across various health behaviors including quitting smoking and attending cardiac rehabilitation, and a patient's failure to adhere to these important behaviors is associated with increased mortality.<sup>4</sup> A multifaceted treatment approach that targets cardiovascular and psychological processes is necessary at minimum, and more robust treatment is likely needed. Not only does depression contribute to poor outcomes, but it also contributes to poor medication adherence, a likely moderator in the relationship between depression and death in CVD.

## CVD and medication adherence

Medication adherence is the extent to which a patient follows his or her provider's recommendations regarding day-to-day treatment such as medication timing, dosage, and frequency.<sup>28</sup> Medication adherence in CVD patients is often sub-optimal.<sup>29</sup> Rarely, in routine clinical practice,

the clinician measures or targets medication adherence.<sup>30</sup> Following hospital discharge, adherence to cardiovascular medications (eg, statins and  $\beta$ -blockers) seems to steadily decrease.<sup>30</sup> Within HF, estimates of medication adherence range from 40% to 60%, although previous estimates have ranged from 10% to 93%.<sup>31</sup>

## Factors influencing medication adherence in CVD

The factors contributing to medication nonadherence in CVD are not well established.<sup>32</sup> The World Health Organization notes that nonadherence can be preventable (eg, a patient forgetting to take his or her medicine) or non-preventable (eg, life-threatening adverse effects), and health care systems, medical conditions, patients, the therapy itself, and socioeconomic factors can all contribute to medication nonadherence.<sup>33</sup> Nonadherence in CVD is associated with disease-related complications, hospitalizations, disability, and increased mortality.<sup>34</sup> In a sample of HF patients using the medication event monitoring system (MEMS) device, lapses in attention, excessive daytime sleepiness, and two or more daily medication doses predicted steep declines in objectively measured medication adherence.<sup>35</sup> Likewise, New York Heart Association class III patients, individuals with asthma, and individuals with renal disease have been found less likely to adhere to an evidence-based HF medication regimen as assessed by MEMS than those with less severe disease.<sup>36</sup>

Previous research may have underestimated the complexity of adherence behavior. For instance, Brown et al's recent model is one of the first to fully recognize some potential determinants of medication adherence behavior.<sup>37</sup> In this conceptual model of atrial fibrillation, patients' adherence to oral anticoagulants and components include the following: predisposing, moderating, and contextual factors; knowledge base and reinforcement; short- and long-term motivation; personalized system, habit formation, and system adaptation; and a self-efficacy loop.<sup>37</sup> This model encompasses many factors previously considered separately in theoretical models of medication adherence and targeted individually in interventions designed to improve medication adherence.

## Medication adherence and mortality

Medication nonadherence may lead to rehospitalization or death.<sup>34</sup> Among surveyed patients, caregivers, cardiologists, and nurses, respondents noted that better medication adherence likely could have prevented nearly one third of HF readmissions.<sup>38</sup> Wu et al aimed to determine the indicators

of medication adherence that predict event-free survival using MEMS and self-report.<sup>39</sup> The MEMS system assessed several factors, namely the percentage of prescribed doses taken (dose-count); the percentage of days when the correct number of doses were taken (dose-days); and the percentage of doses taken on schedule (dose-time).<sup>39</sup> Dose-count and dose-days – but not self-reported adherence – predicted event-free survival.<sup>39</sup> Follow-up analyses determined that the five most commonly cited barriers in the study were cost, “forgetting the time of medication,” “not carrying the medication when I am out,” “amount of pills that I need to take that day,” and “belief that I'll be fine even though I skip one dose of medication.”<sup>40</sup> Of note, the discrepancy between self-reported versus objective adherence highlights that the types of measurement used within research have serious implications for what is already known about medication adherence, and outcomes of certain levels of medication adherence, in CVD.

## Measurement of medication adherence

### Methods of measurement

Adherence methods are either direct or indirect. Direct methods include directly (visually) observed therapy or measurement of a biological marker, level of medicine, or metabolite in the blood.<sup>41</sup> These methods have limited practicality within routine clinical use.<sup>30</sup> Indirect methods include patient questionnaires, pill counts, verbal self-reports, electronic medication monitors, measurement of patient diaries, rate of prescription refills, and assessment of the patient's clinical response.<sup>41</sup>

Most indirect measurement types have drawbacks. For example, although pill counts are easy to perform, timing of medication administration is not captured, and hence, the results are easily manipulated.<sup>30</sup> Electronic pharmacy data (eg, tracking individuals to determine whether they procure their prescriptions) require individuals to obtain medications from a closed pharmacy system, which however fail to capture dose timing.<sup>30</sup> Self-report measures are a convenient alternative, but can be biased by social desirability.<sup>30</sup>

Many researchers justify using self-report adherence because previous studies have found self-reported adherence to be predictive.<sup>42</sup> It tends to have high specificity, but low sensitivity.<sup>43</sup> However, recent research suggests that objective measures may be necessary for accurate adherence measurement in complex disease such as CVD.<sup>44</sup> According to a meta-analysis, correlations between adherence rates measured by self-report questionnaires and MEMS are much

lower in CVD-related conditions like hypertension than in other diseases like HIV/AIDS;<sup>44</sup> this may be due to the complex nature of CVD self-management. Yet, in routine clinical care, providers rarely have the time to accurately measure medication adherence; this suggests a need for enhanced measurement systems and a team-based approach to self-management.

One of the most popular forms of medication adherence telemonitoring is the use of a MEMS cap, a medication pill bottle with a microchip-equipped lid that passively measures medication adherence by date- and time-stamping electronically during each bottle-opening event.<sup>45</sup> MEMS caps may be a useful tool in routine clinical care when used appropriately, although they are not without impediments like any other measurement system. However, limitations of MEMS caps are reactivity and technological failure.<sup>45</sup> Consequently, researchers should use a 1- or 2-month run-in period to minimize measurement reactivity; corroborate MEMS data with another measure of adherence; report MEMS data continuously or use cut-offs determined by pharmacological properties and consequence of nonadherence to the medication; assess MEMS data using multilevel modeling; and properly train patients to use MEMS to improve their accuracy as an adherence measurement tool.<sup>45</sup>

Dichotomizing adherence is likely inappropriate in CVD patients.<sup>46</sup> Researchers frequently dichotomize adherence based on a convention from the HIV/AIDS literature in which  $\geq 80\%$  is considered “adherent” because it is thought to provide optimal virologic suppression.<sup>30</sup> The proper cut-off point should be determined for each medication formulation and the specific disease condition.<sup>30</sup> But a recent study found that low-density lipoprotein cholesterol and blood pressure continue to reduce with adherence levels exceeding 80%, suggesting that the optimal medication adherence level for cardiovascular conditions may exceed 80%.<sup>47</sup> Given Wu et al’s finding that HF patients maximized event-free survival by adhering to their medications at an 88% rate,<sup>46</sup> CVD patients may need to exceed 80% adherence to improve quality of life and outcomes.

Future studies that use an 80% cut-off point should also report continuous adherence values.<sup>30</sup> This is an extremely important factor because many previously reported findings have been interpreted using an unsubstantiated practice (ie, false dichotomization), which has inappropriately shaped findings and clinical practice. For the sake of sound methodology and patients’ lives, empirically derived cut-off points are the only points that a researcher should use in cases where adherence is not reported continuous.

## Comparing methods of medication adherence in CVD

### Comparing self-report to MEMS caps

Studies comparing CVD patients’ self-reported and objectively measured medication adherence have demonstrated significant differences in adherence levels based on the strategies used to measure medication adherence. Previous studies have found a correlation between self-reported adherence and adherence measured by MEMS caps, though not in CVD.<sup>44</sup> In a sample of 68 outpatients, most patients (67%) overestimated their compliance when they used self-reported diaries, and an average of 30% of the self-reported diary entries were errantly recorded compared with the objective MEMS-produced data.<sup>48</sup> Similarly, a study of hospitalized cardiac patients employed electronic monitoring and found adherence rates three times lower than in a study that utilized self-report, which suggests that CVD patients dramatically overestimate their self-reported adherence.<sup>49</sup> In another comparison of self-report to objectively measured medication adherence, HF patients claimed to adhere to their medications 100% of the time; however, according to MEMS, only 76% of patients adhered to their medication at least 88% of the time. Thus, patients’ estimated values do not necessarily predict medication-taking behavior, and individuals with CVD may have difficulty accurately predicting their true rate of medication adherence.<sup>50</sup> This further corroborates the notion that patients with complex diseases need objective measurement tools to accurately assess the quality of their self-management, and they need care systems that target barriers to adherence through a comprehensive team approach.

### Present paper

This paper reviews the literature on depression and objectively measured medication adherence in adult CVD patients. Based on the findings, the paper outlines a model that can serve as a solution to the current challenges.

### Methods

The authors searched in PubMed and Google Scholar starting in April 2014 and limited search results to articles published in the past 20 years. They searched for studies that objectively measured medication adherence in CVD (eg, electronic monitoring, pill counts, and biological measures). The authors repeated their searches periodically (twice in 2015 and 2016 each) up until manuscript submission. The authors searched PubMed and Google Scholar using variants and combinations of the terms “depression,” “depressive symptoms,”

“CVD,” “medication adherence,” and “objective.” Initially, one author independently screened titles and abstracts to determine inclusion status; a second author verified the information after the first author completed the screening. If the second author found an article that met the team’s inclusion criteria, then the first author searched that the reference list of that article for additional relevant studies. This process quickly reached a saturation point in which no new sources were found. In addition, the database search yielded thousands of blatantly irrelevant sources through Google Scholar. After sorting by relevance, the first author stopped screening articles when >100 consecutive articles were identified as being obviously irrelevant.

The authors also searched manually in the following key journals for additional relevant articles: *JAMA*, *Circulation*, *Heart & Lung*, *The Journal for Cardiovascular Nursing*, *European Heart Journal*, and *Patient Preference and Adherence*. However, likely due to the number of articles already screened for inclusion, this process did not result in finding additional articles that were finally included in the team’s results. Hence, numerous relevant articles were excluded (eg, focused solely on hypertension).

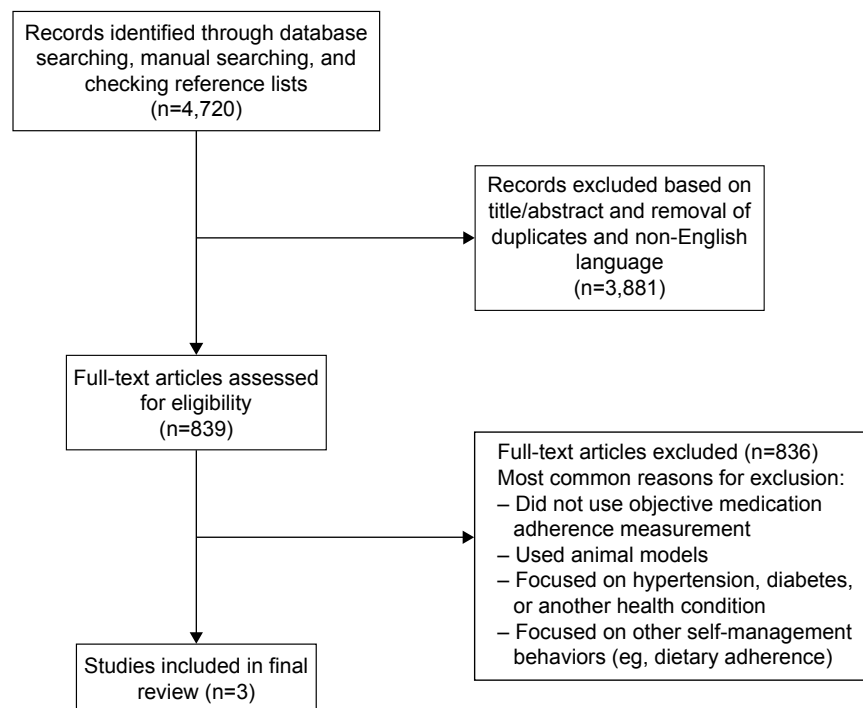
Included articles focused on medication adherence in CVD patients using objectively monitored medication adherence. For the purpose of this study, the team defined “medication adherence” as the amount of prescribed

medication a patient took relative to the entire prescribed (or monitored) regimen.

The researchers most frequently excluded papers that used self-reported adherence, used animal models, or examined solely hypertension. The researchers may have missed some studies that met those criteria, particularly if the studies were not translated into English. Also, although other self-management behaviors are likely influenced by depression and affect outcomes, such as adherence to a low-salt diet, those behaviors far exceeded the scope of this paper, and thus studies focusing on other self-management behaviors were excluded.

Although previous reviews have looked at these topics separately, particularly using self-reported medication adherence, this paper aims to comprehensively summarize the literature using only the objective measures of medication adherence that seem to be most accurate in CVD patients. Given the limited research available using objective medication adherence techniques, the researchers created this review but were informed by a scoping<sup>51,52</sup> rather than narrative framework. Furthermore, the search methodology was informed by PRISMA guidelines<sup>53</sup> to enhance the quality of the review, but the available literature and scoping approach limited the researchers’ ability to strictly adhere to those guidelines.

After screening and removing extraneous or unrelated studies, the researchers included three studies. Figure 1 shows



**Figure 1** Flow diagram of study selection.

the paper selection process. The researchers did not attempt to conduct a meta-analysis of the findings because of the small number of studies found and differences in methods of reporting medication adherence (ie, dichotomized reporting vs continuous values).

## Results

### The relationship of depression and medication adherence in CVD

Depression complicates CVD patients' ability to properly adhere to their medications and to comply with recommended health advice. For example, depression predicts failure to complete a 12-week phase II cardiac rehabilitation program.<sup>54</sup> Persistent depressive symptoms are associated with poor adherence to health behaviors<sup>4</sup> and high risk for mortality.<sup>27,55</sup>

A landmark study by Carney et al in 1995 examined the relationship between major depression and medication adherence in 55 older adults with CVD. The study involved a depression diagnosis assigned by diagnostic interview and objective adherence to 81 mg aspirin measured by an unobtrusive electronic monitor.<sup>56</sup> Nondepressed patients adhered to their medications 69% of the days when they were monitored, but depressed patients adhered to their medication only 45% of the days monitored. The study showed clinically significant differences between depressed and nondepressed CVD patients' adherence to a vitally important cardiac medication.<sup>56</sup> Depression clearly harms self-management in CVD.

Another study that assessed the relationship between depression and medication adherence tested whether reductions in depressive symptoms preceded improved adherence to aspirin over 3 months in 172 acute coronary syndrome patients.<sup>49</sup> In that study, researchers measured aspirin adherence using MEMS, and they assessed depression with the Beck Depression Inventory (BDI) during hospitalization and 1 and 3 months after hospitalization. Using MEMS, adequate adherence was defined as taking aspirin as prescribed at least 80% of the monitored days. Depression severity was associated with nonadherence in a gradient manner: 15% of nondepressed, 29% of mildly depressed, and 37% of moderately to severely depressed patients were nonadherent. The study determined that severely depressed patients were 3.7 times more likely to be nonadherent than nondepressed patients after controlling for potential confounders. Furthermore, adherence increased in patients whose depressive symptoms improved, and it decreased in patients whose depressive symptoms worsened.<sup>49</sup>

According to follow-up analyses, the mean percentage of days when patients properly adhered to their aspirin regimen was lower among persistently depressed patients than in remitted depressed and persistently nondepressed patients.<sup>57</sup> These results remained after controlling for medical comorbidities and baseline depressive symptom severity. Patients whose BDI scores remitted below 10 after 3 months post-hospitalization adhered more than persistently depressed patients, and they ultimately became equally as adherent as persistently nondepressed patients.<sup>57</sup> However, improvements in depression did not show perfect adherence rates, suggesting that other factors influence this relationship.

The relationship between depression and medication adherence in CVD is complicated and seems to be moderated by additional factors. Treating depression alone is unlikely to completely improve medication adherence, and one-dimensional approaches have been largely unsuccessful at modifying this relationship. As the integrated care approach gains popularity and dissemination, the scientific community will likely better understand that the integrated care treatment model is ideally constructed to address this major clinical problem. Future research should determine whether the integrated care model improves health and reduces costs for patients and health care systems; significant progress in CVD management could result from a shift in health care delivery models.

## Discussion

In the United States, currently, CVD is the leading cause of death of American adults,<sup>1</sup> and many CVD patients experience depressive symptoms. However, attempts to reduce depressive symptoms through pharmacotherapy and psychotherapy have not considerably reduced mortality rates. This is likely because depressive symptoms tend to impede ideal adherence behavior, which contributes to poorer outcomes, including mortality. Nevertheless, simply targeting medication adherence behavior may not resolve this association and completely improve outcomes. Instead, moderating factors (eg, the medical regimen's complexity) likely influence the relationship between depression and medication adherence in CVD.

Managing the CVD patient is a responsibility that extends beyond a single provider. Instead, treatment providers should adopt a team-based, integrated approach for addressing associated medical, psychosocial, and cultural processes.

### Integrated care: a possible solution

At present, 20% of primary care office visits are mental health-related,<sup>58</sup> and depression goes undetected in >50% of

primary care patients.<sup>59</sup> Providers rarely address adherence during outpatient health care appointments, and practitioners sometimes assume that the patients are taking their medications as prescribed.

In an integrated care health care model, primary care and behavioral health clinicians work synchronously with patients and families in a systematic, cost-effective manner. Their shared objective is to provide comprehensive patient-centered care and to address both the patient's physical health and behavioral health needs.<sup>60</sup>

### The Affordable Care Act

The Patient Protection and Affordable Care Act (hereafter referred to as the Affordable Care Act) encourages providers to integrate physical and behavioral health services, which helps them to deliver care more coherently and to reduce excess costs. This benefits both patients and health care providers. For example, as many individuals struggle to accurately describe their health history to different practitioners, integrated care can reduce issues in physical and mental health treatment stemming from limited cross-coordination. The Affordable Care Act also allows for increased coverage of home-based health care. This represents an extension of the patient-centered medical home, a model of delivery focused on patient-centered, coordinated health care through a team of health care providers led by the patient's primary care physician.

### Integrated care teams

Patient-centered, integrated care teams have already shown significant promise. The Veteran's Health Administration (VHA) has implemented an integrated care model throughout its system with great success. Changes in service delivery resulting from the VHA's integrated health care model have led to improved recognition of mental health issues in primary care patients, delivery of evidence-based care, and patient engagement in mental health services.<sup>61</sup> In addition, among high-risk, complex patients, the patient-centered medical home system seems to be associated with improved chronic disease management and outcomes.<sup>62</sup> Furthermore, establishing a health behavior coordinator position at each Veterans Affairs hospital has helped to implement integrated care in veteran's services by providing training to primary care physicians, physicians' assistants, nurses, and other health care providers. Additional integration of physical and behavioral health services may increase the delivery of evidence-based mental health treatment and could possibly begin to address mental health issues that often interfere with adherence to

medical interventions in primary care settings. Although this system is working well in the VHA, and despite its promise for complex, sick patients, the broader health care community has been slow to adopt a truly integrated model.

The typical integrated care team's structure is a collaborative system in which each member contributes his or her expertise to shape patient care. Each provider on the team can contribute to improving treatment adherence and self-management among CVD patients. Table 1 provides examples of unique contributions that each team member can make to provide depression and poor medication adherence in CVD patients. Although physicians could refer patients with depression to additional services that address both the depressive symptoms and their effects on self-management, these patients' needs would be best met by an assembly of specialty service providers who work together toward numerous treatment targets.

Furthermore, the most likely course of CVD involves disease progression that over time requires more care and intervention to maximize the chance of survival; creating these treatment teams early on may improve a patient's outcomes. That is, it could improve the quality of life, prolong longevity, and decrease health care expenditures by preventing unnecessary rehospitalization due to poor self-management and delaying need for surgical intervention. Ideally, treatment teams would be composed of as many of the following as possible: a primary physician (primary care or specialty), a physician's assistant, one or more advanced practice and registered nurses, a psychologist, a psychiatrist, a social worker, a dietician, one or more physical and occupational therapists, and a pharmacist. As represented in Table 1, each member would function in a unique role to improve the patient's overall health and well-being, and each member could contribute meaningful care to reduce depression and improve self-management. Furthermore, some responsibilities could be shared among group members, as described in Table 2. In addition, as the integrative team continues to collaborate, it may become necessary to clarify roles over time and update other less-involved team members (eg, outside consultants) with changes to the treatment plan or clinical status. Medical students and residents should be appropriately trained in the integrated care model during the course of their medical training, while established practitioners should be provided with appropriate continuing education opportunities. As is the case with any framework shift, some practitioners may be resistant to changing protocols and may require additional information about how integrated care can benefit both providers and patients, or they may require additional incentives (eg, financial incentives).

**Table 1** Role of integrated care team members in targeting depression and medication adherence in CVD patients

Type of professional	Role in integrated care team members in targeting depression and medication adherence in CVD patients
Primary medical doctor and physician's assistant	<ul style="list-style-type: none"> <li>• Monitor cardiac status</li> <li>• Diagnose medical conditions</li> <li>• Prescribe medications for mental health, CVD, and other health conditions</li> <li>• Monitor symptoms and side effects of medications</li> <li>• Perform or refer patients for procedures necessary for disease management</li> <li>• Educate patients about strategies for preventing future disease and disease progression</li> <li>• Modify patients' overall treatment plan based on a stepped care approach</li> <li>• Refer to consultation with specialists as necessary, particularly to psychiatry if depression does not respond to depression management protocol</li> </ul>
Advanced practice and registered nurse	<ul style="list-style-type: none"> <li>• Monitor cardiac status</li> <li>• Monitor other medical co-morbidities</li> <li>• Medication management through pre-filling pill boxes, clarifying medication instructions, and collaborating with patient to arrange medication schedule</li> <li>• Monitor for precipitants of rehospitalization, including depression</li> <li>• Facilitate mail-order refills or pharmacy reminders and other tools to ensure that patient does not run out of medication</li> </ul>
Psychologist	<ul style="list-style-type: none"> <li>• Treat mental health, particularly depression and health-interfering behaviors such as excessive rest periods following pain flare-ups or emotional eating</li> <li>• Increase medication adherence through motivational interviewing, interventions to manage cognitive impairment, CBT, and ACT</li> <li>• Monitor and test for cognitive factors that may be limiting self-management; refer for neuropsychological testing as necessary</li> <li>• Clarify gaps in health literacy or patient understanding of their conditions, medications, and treatment options</li> <li>• Engage family in patient's treatment by providing recommendations for how the family can contribute to their loved one's health</li> </ul>
Psychiatrist	<ul style="list-style-type: none"> <li>• Evaluate patient for medication if referred from primary doctor or physician's assistant</li> <li>• Consider ways to simplify the regimen and finally improve medication adherence</li> <li>• Engage families in patients' treatment by providing recommendations on how they can support their loved one's mental health</li> <li>• Provide psychoeducation about proper ways to take medication</li> <li>• Evaluate for need of higher level of care (eg, inpatient psychiatric hospitalization) and facilitate with admitting attending if necessary</li> </ul>
Social worker	<ul style="list-style-type: none"> <li>• Case management</li> <li>• Screen for poor mental health, poor self-management, poor diet, cognition, and sedentary lifestyle</li> <li>• Provide supportive counseling as necessary</li> <li>• Measure mental and physical health frequently to shape the course of treatment</li> <li>• Secure patient access to community resources that can improve patient's longevity and quality of life</li> <li>• Manage financial burden of disease management with patient</li> </ul>
Dietician	<ul style="list-style-type: none"> <li>• Provide psychoeducation about proper CVD diet</li> <li>• Monitor for dietary intake that is contraindicated with prescribed medications and supplements</li> <li>• Collaborate with patient and family to meet patient's dietary goals over time</li> </ul>
Physical and occupational therapist	<ul style="list-style-type: none"> <li>• Prescribe physical activity plan that reflects patient's willingness, preference, and ability to be physically active</li> <li>• Monitor for sedentary behavior and use brief targeting interventions with goal-setting to help patient achieve physical activity goals</li> <li>• Monitor for behavioral inactivation or physical agitation (particularly as a symptom of mental health disturbance)</li> <li>• Assess for motor problems that may negatively influence self-management (eg, poor fine motor skills that make getting pill bottles open difficult)</li> <li>• If possible, treat for motor difficulties, chronic pain, etc to restore functioning</li> </ul>
Pharmacist	<ul style="list-style-type: none"> <li>• Monitor for drug reactions and lab levels that suggest a medication adjustment may be necessary, particularly following medication changes and rehospitalization</li> <li>• Collaborate with other prescribing providers to simplify the regimen as much as possible</li> <li>• Monitor for mental health symptoms that may be a consequence of another medication</li> <li>• Revise medication regimen to minimize adverse effects and optimize efficacy</li> <li>• Ensure patient and family are aware of medications, dosages, and potential side effects</li> </ul>

**Abbreviations:** ACT, acceptance and commitment therapy; CVD, cardiovascular disease; CBT, cognitive behavioral therapy.



**Table 2** Shared responsibilities of integrated care team members in targeting CVD patients' depression and medication adherence

Patient care	<ul style="list-style-type: none"> <li>• Monitor for overall safety (eg, fall risk, suicidal ideation, and medication interactions)</li> <li>• Maintain an up-to-date treatment plan, electronic patient health record, and resource list for patient and family</li> <li>• Maintain patient's health, family, and community as the guiding point of all care decisions</li> </ul>
Collaboration with treatment team	<ul style="list-style-type: none"> <li>• Connect patient to acute care when needed and facilitate case coordination with emergency or hospital providers</li> <li>• Encourage increased patient accessibility to care through an electronic health record, a patient portal, after-hours or weekend visits, and home visits when safe and appropriate</li> <li>• Meet as a team to quantify patient's progress and revise the treatment plan to include outside providers as appropriate</li> </ul>
Collaboration with patient and family	<ul style="list-style-type: none"> <li>• Introduce and revisit advance directives and health care goals with the patient and family</li> <li>• Collaborate with the patient and family to reduce hospitalization and improve quality of life</li> </ul>

**Abbreviation:** CVD, cardiovascular disease.

Furthermore, telemedicine could unite practitioners to form teams across rural or underserved areas; future policy development is necessary to allow for comparable reimbursement of these services. Integrated teams with adequate resources should ideally conduct outcomes and cost-effectiveness research so that these data can be used to justify policy shifts and a change from a fee-for-service model to one that supports interdisciplinary chronic disease management.

### Feasibility

Given the ways in which health care systems are changing in the United States and worldwide based on policy changes, electronic health records, and other care innovations, this approach will likely become more feasible over time. For example, the Affordable Care Act is facilitating a movement to expand integrated care services in community primary care settings. Several studies have already demonstrated the feasibility of integrated care in HF,<sup>63</sup> diabetes,<sup>64</sup> and stroke.<sup>65</sup> These studies indicated that an integrated care team produced up to a 70% increase of patients taking a more active role in their health care,<sup>64</sup> improved patient outcomes (eg, blood pressure, cholesterol, and quality of life),<sup>64,65</sup> and improved satisfaction from staff and patients,<sup>64</sup> contributing to lower admissions rates by 20% and lower health care costs.<sup>63</sup> In addition, the VHA already has a model for patient-aligned care teams and health behavior coordinator positions to increase patient-provider partnership in care and provide health behavior change training to clinical staff. Such programs have been successful thus far and serve as models for other health care providers.

Integrated care benefits not only providers (through better communication, medical management, health education, and case coordination) but also patients (through increased convenience, decreased stigma, higher quality care, and quicker appointments).<sup>66</sup> Given the changing health care system, the population's increasing longevity

and medical complexity, and the demands of coaching patients to achieve adequate self-management, the research community should further explore integrated care systems and evidence-based practice as exemplary opportunities for reducing depression, increasing medication adherence and other components of self-management, and leading the field toward improved quality of life and outcomes in individuals with any chronic illness.

### Potential interventions

Numerous available interventions target medication adherence behavior. A multidimensional, tailored approach that targets health literacy, encourages self-monitoring, utilizes automatic alerts when prescriptions are not filled on time, and employs blister packs and pill boxes may improve adherence in adults with CVD and other chronic illnesses.<sup>28,67</sup> However, discrepancies exist in the literature. Some studies report that electronic objective monitoring burdens and challenges individuals with CVD.<sup>68</sup> However, although it may seem counterintuitive that CVD patients, and particularly older patients, can handle electronic monitoring, feasibility studies suggest they can.<sup>69</sup>

Health care professionals may also find that interventions using phone counseling or nurses as case managers in primary care may also be effective and feasible, as the interventions are short and do not require patients to leave their homes.<sup>70</sup> Studies have associated such interventions with improved depression for individuals.<sup>70,71</sup> Other treatments include antidepressants, CBT, physical activity, and cardiac rehabilitation programs.<sup>72</sup> Motivational counseling may be another effective method for improving adherence in CVD patients.<sup>73,74</sup> Antidepressants are also available, but it is important to note that SSRIs are preferable to tricyclic antidepressants because of the latter's significant cardiovascular side effects.<sup>75</sup> Further randomized clinical trials are needed to determine whether SSRIs, psychotherapy, or both can reduce cardiac events and mortality in CVD.<sup>76</sup>

In addition, interventions can target different populations to maximize success. Interventions that target nonadhering patients may have a larger effect on medication adherence<sup>77</sup> and be more cost-effective than other studies. Programs that target both the patient and the caregiver, especially significant others, in improving health behavior of CVD patients<sup>78</sup> may produce sustainable improved outcomes.

## Overall limitations

A major methodological issue limits the medication adherence research literature: many well-designed studies rely on self-reported adherence behavior.<sup>79</sup> As evidenced in the present research, self-reported estimates of medication adherence may overestimate medication adherence behavior in complicated chronic illnesses such as CVD.<sup>44</sup> Future research should measure adherence objectively (eg, through pill counts or electronic monitoring). However, electronic devices also suffer from limitations such as “fake” medication-taking behavior to silence an alarm or a patient misplacing the medication after the device has already recorded a medication-taking event. Future technological designs should attempt to minimize discrepancies between a technologically documented event and real-time medication-taking behavior.

As previously stated, the authors of this study were unable to include papers not published in English, and future reviews should examine research conducted in non-English-speaking countries, if possible, to better understand the worldwide literature to date.

## Future research

The health care research community has advanced exceptionally to understand the relationship between depression and medication adherence, and future research will dramatically affect clinical settings. Clinicians need easy, systematic, and noninvasive screenings for depression and medication adherence to use in outpatient cardiology routine visits.<sup>80</sup> Quick-targeted interventions using stepped care are also needed and will likely incorporate large, well-powered trials of antidepressants and psychotherapies.<sup>81</sup>

In addition, many current medication adherence measurement strategies are expensive (eg, MEMS),<sup>33</sup> and accessible interventions will need to be cost-effective and widely available. As the pathophysiological link between depression and CVD remains unclear, there is a similar lack in pharmacotherapy that targets the dysregulated physiology that might help explain the increased morbidity and mortality in patients with both CVD and depression.<sup>82</sup> Therefore, future

pharmaceutical and behavioral research can target this link as a point for intervention.

## Overcoming methodological issues

Future research must address methodological issues. The field should develop a consistent method for reporting medication adherence, as comparing adherence rates across studies and conditions remains difficult.<sup>30</sup> Moreover, the present review only incorporated high-quality publications using objective measurements; readers should use caution to evaluate the quality of the evidence and the methodology and inclusion criteria while reading other reviews in this area. Furthermore, interventions continue to focus on a single disease, but a typical patient takes multiple medications for various conditions.<sup>28</sup> Future interventions should provide a menu-driven, patient-centered approach to maximize the extent to which research translates to real-world nonadherence problems; menu-driven, patient-centered approaches can easily be tailored to the individual and address a wide variety of self-management challenges.<sup>28</sup> In addition, prospective studies are needed to understand directionality and determine whether poor medication adherence causes individuals to become depressed. Prospective studies must determine the specifics of nonadherence behavior, which may include failure to begin, execute, or continue the regimen. In light of great advances of medicines in the past decade, future research should target methods in which health care providers can encourage patients to take their medications as prescribed.

## Directions for future research in integrated care

Much work in integrated care is still needed. Further studies on the feasibility of integrated care teams would help identify the team's place in the health care structure and its impact on the overall health care costs. In addition, existing integrated teams could provide the field with valuable data on patient outcomes and cost-effectiveness to better support interdisciplinary chronic disease management. As integrated care transitions from idea to practice, continued research is needed to understand the impact of a team-based approach on depression, quality of life, and outcomes. Future research should identify the most salient team components that are responsible for long-term improvements in self-management. Further, as technology continues to revolutionize health care practice, future research should examine the barriers and opportunities for technology's role as a tool in improving care.

Ongoing dissemination and implementation of integrated care systems should embody an iterative process in which all key stakeholders are involved, including patients and their families. Programs should be realistic, capitalize on the team's strengths, and be aspirational in nature. Finally, even with the integrated care model's increasing popularity, many patients remain underserved. Therefore, providers and governments should target health disparities to reduce health-related inequities across communities and patient populations.

Although depression and poor medication adherence are difficult to detect and repair, both are modifiable risk factors for decreased event-free survival in CVD. However, simply treating depression does not perfect medication adherence, just as targeting poor medication adherence does not resolve depression. Many of the moderating factors that influence the relationship are either modifiable or easy to detect. Although the depression–adherence relationship is complex and poorly understood currently, future research may illuminate the etiology of the relationship and the proper intervention that will improve CVD patients' quality of life and outcomes.

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