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Interventions to Enhance Adherence to Medications in Patients With Heart Failure
A Systematic Review

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Prognosis remains poor for patients with chronic heart failure (CHF), despite improvements in the prevention and treatment of heart failure over the last 25 years. Recent estimates indicate that the median survival after a first episode of heart failure is 2.3 years for men and 1.8 years for women.[1] It is suggested that the improvements in outcomes that have been achieved can be partly explained by increases in prescribing rates of medications such as angiotensin-converting enzyme inhibitors,[2] β-blockers,[3] and spironolactone[4] over this period.[1] Although the evidence on medication efficacy for certain subgroups of patients with CHF is clear, there are also compelling data showing that many of these patients do not take their medications as prescribed by health care providers.[5,6] This "nonadherence" to medication therefore remains a significant barrier to enhancing the effectiveness of existing treatments.

Estimates for nonadherence to medications in CHF have varied widely.[5] One of the largest studies found that only 80% of patients with a prescription for angiotensin-converting enzyme inhibitors at hospital discharge completed the prescription form 30 days after discharge, and this rate subsequently fell to 60% over 1 year.[7] Full adherence, defined as filing enough prescriptions to have daily medication available for 1 year, may be as low as 10% in CHF.[8] Poor adherence to medication in CHF is associated with worse outcomes in observational studies, including shorter event-free survival.[9] Therefore, strategies to enhance adherence provide a potentially valuable strategy for improving survival, reducing hospitalization and managing patient symptoms in CHF.

In this report, we provide an up-to-date review and analysis of those studies that have developed and evaluated medication adherence interventions in CHF. Because CHF is typically symptomatic and includes medication with actions that are discernible to the patient within hours of ingestion, for example, diuretics and consequent diuresis, an examination of interventions for this population in isolation from cardiovascular disease populations more generally is warranted because some CVD patient populations can have asymptomatic conditions, for example, hypertension or hyperlipidemia and medication regimens with little or no side effects.[10] Previous reviews[11] may have also set inclusion criteria that may be too stringent for CHF populations, in which high morbidity and mortality rates can make attrition rates for medication adherence outcome measures appear abnormally high over 1 year even in high-quality studies, for example, >80% participant follow-up and >6 month follow-up inclusion criteria.[11] Therefore, potentially useful studies may have been overlooked in previous reviews. The objective of this systematic review was to identify and summarize the effectiveness of intervention strategies to enhance adherence to medications in heart failure populations.

Study Selection
The following inclusion criteria were used to identify appropriate published studies for the review:

(1) The study design was a randomized, controlled trial in which an intervention group was compared with treatment as usual or a clearly justified comparison group.
(2) The population of interest comprised adults (>18 years old) with a diagnosis of heart failure confirmed by a physician.
(3) The intervention strategy clearly had a primary or secondary aim to increase adherence to medication prescribed for heart failure.
(4) Self-administered medication, that is, medication not administered by a health care professional, was measured as an outcome by any of the following methods: pill count, electronic monitoring, refill or prescription records, and self-reported data.

A trial was included if it met all our inclusion criteria. Reference Manager (version 11) software was used to identify and extract duplicate studies.

Literature Search
We performed a systematic review, using guidelines developed by the Cochrane Collaboration. The databases of the

Table 1.   List of Individual Intervention Techniques Specified in the Reviewed Studies

Simplification of the medication regimen/consolidation of the medication regimen[17,20,25,30]

Patient education—individual[15–17,19,20,23,25,26,29]

Patient education—in groups[28]

Family education[23]

Self-monitoring of symptoms[17,18,25,28,29]

Self-monitoring of adherence[17,18,25,28,29]

Health care provider monitoring of symptoms directly[7,20,25]

Health care provider monitoring of symptoms remotely[18,20,21,23,24,26]

Health care provider monitoring of medication adherence directly[16,27]

Health care provider monitoring of medication adherence remotely[18,21–24,26]

Telephone/video telephone prompts to take medication[27,29]

Enhancing communication and coordination of patient health information between health care providers[17,18,22–26]

Enhancing motivation to take medications[16–20,23,25,29]

Knowledge and skills assessment[16,19,22,24]

Medication dispensing[24]

Verbal instruction[16,17,19,20,23–25,27]

Environmental restructuring[18,28]

Eliciting social support in the community[18,28]

Eliciting support from health care providers[15,25,26,29]

Cognitive restructuring[28]

Relaxation[28]

Barrier identification[28]

Coping planning—planning to overcome barriers[28]

Cochrane Central Register of Controlled Trials, MEDLINE, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Embase, and PsychInfo were searched for full published reports to the end of December 2010. All databases were searched from their start date. The search strategy incorporated relevant terms from recent Cochrane Reviews on adherence to medication[11,12] and heart failure,[13] and a highly sensitive search strategy developed by the Cochrane group for maximizing the identification of randomized trials was also applied in Medline.[14] The reference lists of all selected articles and relevant review articles were also searched for additional studies. Only studies/abstracts in English were included because translation services were not available to the authors for this review.

Data Extraction
Data were extracted from selected studies with the use of a predefined form. Data were extracted by Dr Molloy. Risk of bias was assessed independently by Drs Molloy and O'Carroll, and discrepancies were resolved by discussing the discrepant judgments. Details of information extracted are provided in Tables 1 and 2. Study authors were contacted for additional information.

Quality Assessment
As recommended by the *Cochrane Reviewers Handbook,*[14] we assessed study quality according to 4 main sources of potential bias in the identified studies: (1) selection bias, (2)

performance bias, (3) attrition bias, and (4) and detection bias. To do this, studies were assessed for adequate sequence generation and allocation concealment (selection bias), the presence of blinding in outcome assessment (performance and detection bias), and whether reporting of losses to follow-up and intention-to-treat analysis were specified (attrition bias). Selective reporting bias was not assessed because few studies had published protocols before completing and reporting their studies, making assessing this aspect of bias difficult in most cases. The overall quality assessment for each study was summarized by using a risk-of-bias summary figure, based on Cochrane review recommendations.[14]

Analysis
Pooling of the data was not possible because of the heterogeneity of measurement and analysis between studies. We grouped studies according to the main components included in the interventions. This was based on categories specified in a recent systematic review of interventions to enhance adherence to lipid-lowering medication.[12]

Selection of Trials
In total, the search strategies identified 1660 records (after removal of duplicate records) of potential relevance from searches of all 5 electronic databases (Figure 1). An inspection of study titles and the study abstracts revealed that more than 95% of these did not meet the review inclusion criteria. Fifty-three studies were retained for closer inspection, and only 16 independent studies derived from these studies met all the review inclusion criteria. The flow of studies through the selection process is summarized in Figure 1.

Characteristics of Included Studies
Sixteen randomized, controlled trials were identified, containing data on 3305 patients with CHF. The median total sample size was 144 patients, with a range of 37–902. The majority of studies (9/16) were conducted in the United States. The average age of the study samples ranged from 55 years[15] to 85 years.[16] Male participation in trials ranged from 37%[17] to 99%.[18] The median follow-up time was 6 months, ranging from 2 weeks to 12 months, with 6 of 16 (38%) of studies having follow-up times of less than 6 months. The mean percentage of patients included at follow-up in the 13 studies that provided this data was 79.8%, with a range of 28–100%. Adherence was measured by self-report in 5 studies, the medication event monitoring system in 5 studies, tablet counts in 3 studies, and medication refill records in 3 studies. Because of the heterogeneity of measurement and limitations in reporting, it was not possible to report a summary of baseline rates of adherence for the reviewed studies. Table 1 outlines a list of intervention techniques that could be identified from the reviewed studies. Full details of all included studies are provided in Table 2.

Risk of Bias in Included Studies
All 16 studies reported random allocation; however, there was limited information provided on sequence generation and allocation concealment to evaluate this with confidence for many of the studies in this review. Although double blinding

Table 2.   Summary of Studies That Evaluated Intervention Strategies to Enhance Adherence to Medication in Heart Failure Patients in Randomized, Controlled Trial Designs

	Sample Size Follow-Up (%)	Mean Age, Years (SD) % Male	Adherence Measurement	Follow-Up in Months	Key Study Findings Relating to Adherence
Patient education					
Gwadry-Sridhar[19] (2005) Canada	136 (99%)	C: 65 (12) E: 67 (14) C: 69% E:76%	Heart failure medication refill records.	12	87% intervention group adherent to ACE inhibitor versus 83% control (NS). β-Blockers: 87% versus 85% (NS). Digoxin: 85% versus 81% (NS). Diuretics: 77% versus 77% (NS).
Rich[20] (1996) United States	156 (not provided)	C: 78.4 (6.1) E: 80.5 (5.7) C: 41% E: 26%	Pill counts.	1	Adherence was 87.9% in patients randomized to the study intervention, compared with 81.1% in the control group. An adherence rate of ≈80% was achieved by 85.0% of the treatment group versus 69.7% of the control group. There was a significant difference in adherence between the groups.
Intensified patient care—direct patient contact					
Bouvy[22] (2003) The Netherlands	152 (60%)	C: 70.2 (11.2) E: 69.1 (10.2) C: 60% E: 72%	Medication event monitoring system to measure loop diuretic adherence.	6	Intervention group had fewer days (2%) without use of loop diuretics compared with the usual care group (5%). There was a significant difference in adherence between the groups.
Goodyer[16] (1995) United Kingdom	100 (80%)	C: 85 (5.4) E: 84 (4.5) C: 24% E: 30%	Pill counts.	3	93% of the intervention group was adherent according to pill count at follow-up versus 51% of the control group. There was a significant difference in adherence between the groups.
Laramee[23] (2003) United States	287 (82%)	C: 70.8 (12.2) E: 70.6 (11.4) C: 50% E: 58%	Self-report measure of medication taking on a 5-point scale: 1, never; 5, always.	3	No difference between groups at 4-wk follow-up. Self-reported adherence was significantly higher at 12-wk follow-up in the intervention group.
Murray[24] (2007) United States	314 (86%)	C: 62.6 (8.8) E: 61.4 (7.7) C: 34% E: 32%	Medication event monitoring system to measure taking and scheduling adherence to all cardiovascular medications.	12	Adherence was 67.9% and 78.8% in the control and intervention groups, respectively. These effects dissipated at 3 mo. Medications were taken on schedule 47.2% of the time in the usual care group and 53.1% of the time in the intervention group but this effect also dissipated at follow-up.
Sadik[25] (2005) United Arab Emirates	221 (94%)	C: 58.6 E: 58.7 C: 50% E: 50%	Self-report binary: Yes/No.	12	81% of the intervention group was self-reporting to be adherent at 12 mo versus 34% of the control group. There was a significant difference in adherence between the groups.
Varma[17] (1999) Northern Ireland	83 (28–59%)	C: 76.4 (7) E: 75.5 (6) C: 37% E: 45%	Self-report binary and drug use profiles using patient medication records.	12	No significant difference between the groups in self-reported data. The intervention group had significantly better adherence, 10/13 (77%) versus 3/10 (30%) according to patient medication records; however, only n=23 for this analysis.
Intensified patient care—telephone or telemonitoring					
Antonicelli[21] (2010) Italy	57 (not provided)	C: 79 (6) E: 77 (8) C: 66% E: 57%	Self-reported by telephone. No other detail provided.	12	The intervention group adherence was significantly higher at 89.7% versus 35.7% in the control group. There was a significant difference in adherence between the groups.

(*Continued*)

Table 2.   Continued

	Sample Size Follow-Up (%)	Mean Age, Years (SD) % Male	Adherence Measurement	Follow-Up in Months	Key Study Findings Relating to Adherence
Fulmer[27] (1999) United States	60 (83%)	C: 73.7 (5.3) E1: 76.2 (8.8) E2: 73.1 (6.5) C: ? E1: ? E2: ?	Medication event monitoring system to measure up to 4 heart failure–related medications.	2 wk	The control group adherence dropped from 81–57% between baseline and follow-up, whereas the 2 intervention groups remained stable: telephone, 76–74% and video-telephone, 82% and 84% at baseline and follow-up, respectively. No significant differences between groups were observed.
Jerant[26] (2003) United States	37 (not provided)	C: 72.7 (11.4) E1: 71.3 (14.1) E2: 66.6 (10.9) C: 50% E1: 42% E2: 46%	Nurse log of adherence. No other detail provided. Binary: >75% or ≤75% of doses taken.	6	No significant difference in adherence to medication was observed.
Ross[15] (2004) United States	107 (76%)	C: 55 E: 57 C: 74% E: 80%	Self-report: General Adherence Scale from the Medical Outcomes Study.	12	No significant difference in self-reported adherence to medication was observed.
Wakefield[18] (2009) United States	148 (74%)	C: 67.2 (8.5) Telephone E: 71.8 (10.2) Videophone E: 69.0 (9.6) C: 98% Telephone E: 100% Videophone E: 98%	Self-report: The proportion of medications for which the participant's responses agreed with the directions for use.	6	There were no significant differences between the control (91%) and the intervention groups (86%) at 6 mo.
Complex behavioral approaches					
Powell[28] (2010) United States	902 (70%)	C: 63.4 (13.3) E: 63.8 (13.7) C: 52% E: 54%	Medication event monitoring system to measure ACE inhibitors or (β-blockers if the patient was not taking ACE inhibitors).	12	No difference between groups at follow-up. Both groups decreased adherence by 7%.
Tsuyuki[29] (2004) Canada	276 (100%)	C: 72 (12) E: 71 (12) C: 58% E: 58%	Pharmacy records: Medication possession ratio was calculated based on the No. of days of ACE inhibitor dispensed divided by the No. of days of follow-up.	6	No difference between groups at follow-up in adherence to ACE inhibitors.
Simplification of the drug regimen					
Udelson[30] (2009) United States	269 (91%)	C: 65.5 (12.8) E: 65.1 (11.9) C: 71% E: 77%	Medication event monitoring system to measure carvedilol adherence (5 mo).	5	No difference between groups at follow-up. 89.3% of the control group was adherent versus 88% for the experimental group. Note: Although there were 3 arms in this trial, the primary comparison of interest for the adherence measures was the controlled-release carvedilol with the double-blind twice-daily immediate release formulation; therefore we only focus on this aspect of this study.

C indicates control group; E, experimental group; ACE, angiotensin-converting enzyme; NS, nonsignificant; ?, not provided.
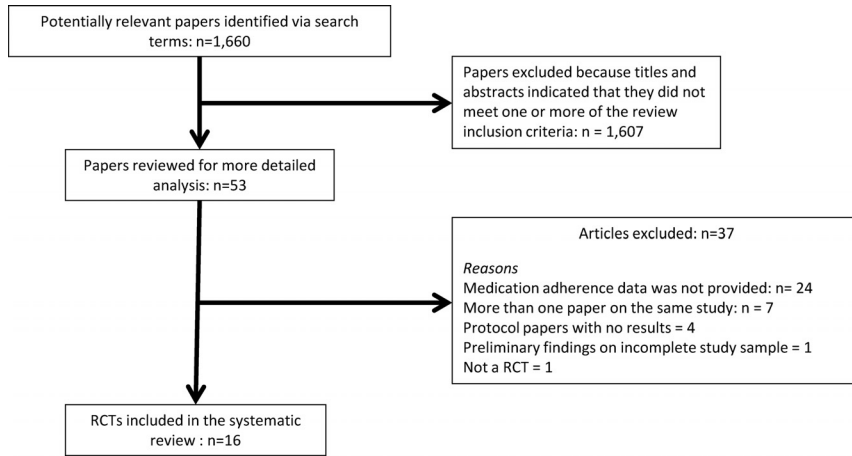
Figure 1. Selection of articles for systematic review. RCT indicates randomized, controlled trial.

is not possible in most behavioral trials, the issue of blinding was addressed in 31% (5/16) of studies. Eleven studies provided information on loss to follow-up, but only 6 studies clearly specified intention-to-treat analyses. Figure 2 provides summary data on risk of bias across the 16 studies.

Types of Intervention

Interventions could be classified into the 4 main categories identified in a recent review of interventions to improve adherence to lipid-lowering medication.[12] It is important to note, however, that several multicomponent interventions could be included in more than 1 of these 4 categories, and a distinct set of intervention strategies categories did not emerge, as can be seen in Tables 1 and 2.

(1) Patient Education and Information
The educational intervention described by Gwadry-Sridhar et al[19] found no evidence that this kind of intervention can lead to enhanced adherence. The multidisciplinary intervention described by Rich et al,[20] which included aspects of education and information provision, found evidence that a multicomponent intervention can lead to enhanced medication adherence. It is important to note that this intervention also incorporated intensified patient care and simplification or "consolidation" of medication regimens.

(2) Intensified Patient Care
The 8 studies that involved intensified patient care can be subdivided into 6 direct patient contact interventions[16,17,22–25] and 5 telephone or telemonitoring programs.[15,18,21,26,27] All 6 of the direct patient contact interventions led to enhanced medication adherence, whereas only 1 of the telephone or telemonitoring programs led to enhanced adherence. Five of the 6 direct patient contact interventions were pharmacist-led.

(3) Complex Behavioral Approaches
The largest study examining interventions to enhance medication adherence in CHF conducted to date found no evidence that that a complex multicomponent intervention that included a range of behavior change techniques led to enhanced medication adherence.[28] A smaller study that also used a complex intervention that included a range of behavior change strategies also reported null results.[29]

(4) Simplification of the Drug Regimen
The single study that attempted to evaluate this strategy on its own did not find evidence of enhanced adherence after a simplification of the drug regimen.[30] Simplification of medication regimens may have occurred in an unsystematic way in some of the other interventions included in this review.[20]

Main Findings

This review found that 8 of 16 randomized, controlled trials identified provide evidence that adherence to medication can be enhanced in patients with CHF. Intensified patient care, particularly involving pharmacists, may be beneficial, as there are at least 5 studies that show intensified care from a pharmacist,[16,17,22,24,25] in conjunction with other health care professionals, leads to better medication adherence in patients

L Low risk of bias
H High risk of bias
? Unclear risk of bias

	Adequate sequence generation?	Allocation concealment?	Were the study groups comparable at baseline?	Incomplete outcome data addressed?	Intention to treat analysis specified?	Numbers of dropouts (with reasons) reported?
Antonicelli (2010)	?	?	L	H	H	H
Bouvy (2003)	L	L	L	L	L	H
Fulmer (1999)	L	L	L	L	H	L
Goodyer (1995)	L	?	L	L	H	H
GwadryHSridhar (2005)	L	L	L	L	H	L
Jerant (2003)	L	L	L	L	?	L
Laramee (2003)	?	?	H	L	H	L
Murray (2007)	L	L	L	L	L	L
Powell (2010)	L	L	L	L	L	L
Rich (1996)	L	L	H	?	L	H
Ross (2004)	L	L	?	L	H	L
Sadik (1995)	L	?	L	?	H	L
Tsuyuki (2004)	L	L	L	L	L	L
Udelson (2009)	L	L	?	L	L	L
Varma (1999)	L	?	H	L	H	L
Wakefield (2009)	L	L	H	L	H	?

Figure 2. Risk of bias summary.

with CHF. There is emerging evidence that patient education and self-management training alone is not effective in enhancing adherence to medication.[19,28,29] The overall conclusion of the methodological quality of the 16 trials included in this review indicate that there is limited high-quality evidence evaluating the effectiveness of specific adherence-enhancing interventions in patients with CHF and that the findings of many of the existing randomized, controlled trials should be interpreted with caution. The heterogeneity in intervention techniques and measurement methodology observed between the studies in this review means that a conclusive literature on enhancing adherence to medication in heart failure has yet to emerge. This mirrors findings from other related broader reviews in a range of clinical conditions.[11,12]

Our assessment of the sample characteristics also revealed that the patients enrolled into these studies were not representative of the patients with CHF seen in clinical practice in terms of age and sex profile. This indicates that selection biases are operating in recruitment in this area of research, which limits the generalizability of these findings. The relatively short and variable follow-up times seen across these 16 studies also show that there are limited data on the sustainability of both the intervention strategies and the intervention effects in those studies that found significantly enhanced adherence. Five of the reports included[23–26,29] incorporated a health economics evaluation with varying degrees of sophistication; therefore the cost implications of most of the intervention strategies are unknown. However, 2 of these studies[26,29] reported significant health care cost reductions as a consequence of the interventions. This raises the possibility that medication-enhancing interventions can reduce health care costs, which may be particularly important in new health care funding environments, for example, accountable care organizations in the United States or the Quality Outcomes Framework in the United Kingdom.

Although a number of studies in this review did include interventions that used information technology, specifically telemonitoring of patients with CHF,[13] this area of research has yet to evaluate the role or potential of electronic patient records or new developments in handheld communication devices and social media to enhance adherence to medication in heart failure. Future work should attempt to investigate the potential of these new technologies in motivating, enabling, and prompting patients with heart failure to take their medications as prescribed.

Limitations

The most obvious limitation in this review was that quantitative meta-analysis was not possible. A recent meta-analysis of 33 studies[31] testing adherence-enhancing interventions for older adults estimated that effect sizes were likely to be in the small to medium range, with a summary standardized mean difference of 0.33 in medication adherence observed between control and intervention groups. Only 1 of the studies in the published meta-analysis is included in our review.[20] Until there is greater consistency of measurement and analysis across studies, we cannot know whether similar effects can be achieved in CHF populations. Future investigators should therefore assume that intervention effects will not be larger

than the small to medium range when conducting sample size calculations for new studies.

The limited number of studies identified that describe a heterogeneous range of interventions prevent us from drawing firm conclusions on many types of adherence promoting strategies for patients with CHF. For example, the null findings for the one study[30] in this review that compared once-daily dosing with twice-daily dosing should be considered in light of the limitations of that particular study and the considerable evidence in other conditions that simplifying medication regimens is associated with better adherence.[32] There was also limited detail provided on the contexts in which interventions were delivered. This makes it difficult to know where and when effective interventions to enhance adherence to medication are best delivered.

Implications for Research

Adherence to medication and other aspects of self-care for a debilitating symptomatic chronic illness such as CHF is a complex behavior with multifactorial determinants,[6,33] including a range of individual and social-environment factors.[34,35] Although earlier studies have reviewed the broader issues of adherence to health professionals' self-care recommendation in CHF,[5] this review focused on those interventions that specifically address medication adherence for 3 key reasons. First, the association between medication adherence and health outcomes is more precisely described,[2,4] whereas the benefits of other aspects of adherence to CHF self-care cannot be estimated with the same degree of precision because of measurement and study design limitations that are inherent in studying these phenomena, for example, weighing oneself daily and limiting sodium intake. Second, adherence to medication is a very different behavioral phenomenon[36] than other aspects of adherence to self-care in heart failure that is likely to have different determinants. Finally, intervention strategies to enhance adherence to medication are likely to be of a different form than many other aspects of adherence to self-care, given the unique barriers and facilitators to this behavior.[5,33] Therefore, there is clearly scope to develop a focus for further investigation into adherence to medication in heart failure as opposed to more generalized management of self-care in heart failure.[5]

Four of the studies included in this review[18,21,28,30] have been published since the Cochrane review of interventions for enhancing medication adherence,[11] and only 1 of the studies[25] included in the present review was included in that Cochrane review. Another more recent relevant review on improving adherence to cardiovascular medication[10] included only 4 studies from the present review.[16,24,27,30]

Many of the reviewed studies provided limited information on the content of the study interventions. This prevents the development of a cumulative body of research or even simple replication of individual studies. The increasing emphasis on publishing detailed protocol reports in advance of the study commencement has reduced this problem in more recent studies. This area of research would, however, be greatly strengthened by the development of a taxonomy of behavior change techniques for medication adherence–enhancing interventions to standardize the content, classification, and

description of intervention strategies. The value of such taxonomies is gaining increasing recognition in other areas of behavioral science that focus on the role self-care in promoting health.[37] Because the content and context of many adherence-enhancing interventions is not clearly specified in standardized terminology and theory from behavioral science is often absent, the approaches to intervention development in this area can be likened to developing antihypertensive medications without any understanding of the pharmacology of the medication, the physiology of systemic blood pressure control, or the pathophysiology of hypertension.[38]

Implications for Practice

There is clearly scope to significantly improve outcomes in heart failure by enhancing adherence to those existing medications that are known to reduce morbidity and mortality from heart failure. CHF medication regimens have become increasingly complex as new treatments have emerged,[6] which provides a challenge for patients with CHF to manage. Practitioners should consider that developing effective methods to increase patient adherence to existing medications with known efficacy could have far greater health benefits than providing new treatments that may not be followed.[11] The reviewed studies do provide evidence that enhanced adherence to medications can be achieved in heart failure patients and that the role of pharmacists may be particularly important, in particular, direct communication between patient, pharmacists, and other health care providers.[22,24,25] This review also suggests that patient education about CHF or self-management training alone may not be effective. Overall it is clear, however, that formal recommendations on the best approaches to enhance adherence to medication in CHF cannot be derived from the existing studies. New studies with more clearly justified and specified methodology are required to generate a cumulative body of findings that could be used to inform clinical practice. In particular, more explicit use of behavioral sciences in developing adherence interventions in CHF is clearly warranted.

Conclusions

It may be possible to improve adherence to medication in patients with CHF by using a range of strategies; however, the specification of effective techniques requires greater clarity in this literature. There is currently limited high-quality evidence on the effectiveness of interventions that aim to enhance adherence to medication in typical heart failure patients, and further research is needed to identify the optimum strategies for implementation in clinical practice.

Disclosures

None.

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