The effectiveness of interventions to manage treatment adherence in adult heart transplant patients: a systematic review protocol

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Review question/objective
The objective of this review is to assess and synthesize the best available evidence on the effectiveness of interventions to manage treatment adherence of adult heart transplant patients.

Therefore, the review question is: in adult heart transplant patients, what interventions are the most effective to manage adherence to pharmacological and non-pharmacological treatments?

Background
Advanced surgical techniques have reduced surgical mortality to less than 5%. Solid organ transplantation, over the last 20 years, has evolved from an experimental treatment to an efficacious treatment alternative for several diseases, including refractory heart failure. 1-3

There has been a significant increase in organ donation rates in Brazil. 4 In the first half of 2010 there were 9.9 donors per million population (pmp), with higher numbers of kidney and liver transplants. Regarding heart transplants, figures have remained stable, with rates ranging between 0.8 and 1.1 pmp. In the first half of 2010, 25 centers had the capability to perform heart transplants in Brazil.

The Global Observatory on Donation and Transplantation 5 reports that in 2009 there were nearly 104,065 transplants worldwide. Of the total, 5,043 were heart transplants, performed in 53 countries. According to the Organ Procurement and Transplantation Network (OPTN) 3 the number of heart transplants has varied. Between 1998 and 2004 the figure reduced (from 2083 to 1724). After achieving
certain stability (2005 to 2008), in 2009, a total of 1853 transplants were performed, which promoted an increase of the transplant indicator (per 100 patients on the waiting list) from 56.9 to 73.3.

Several circumstances could impede the satisfactory evolution of transplants, such as poor socioeconomic conditions, communicable diseases, neoplasms, alcoholism, and the lack of adherence to treatment.  

The concepts regarding adherence vary considerably, with one of the oldest definitions being that by Hypocrites, who advocated the importance of observing the patient's error related to what had been prescribed.  

In general, adherence is defined as the use of prescribed medications or another procedure in at least 80% of the total, observing the correct doses, times, and length of treatment. According to the World Health Organization (WHO) adherence is defined as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations of a health care provider".

The terms adherence and compliance have different meanings, and their utilization by authors reveals their understanding regarding their role in the process. Compliance has a hierarchical connotation, translated as obedience, and denotes the passive role of the patient, whereas the term adherence assumes the free right that people have of choosing to adopt or not a given recommendation.

The abandonment of treatment after organ transplantation is considered to be a relevant health problem, as it contributes to increasing morbidity and mortality, reduces quality of life, and increases costs and patients’ use of health care services. Adherence to immunosuppressive therapy is acknowledged as a predicting factor for a successful outcome. Non-adherence rates range between 20% and 37% in adult transplant patients, occurring in 22.6 cases out of 100 patients/year, and accounting for approximately 50% of the acute rejection cases and 15% of the graft loss.

There are several reasons for non-adherence to treatment, including the adverse effects of the medication, inadequate instructions, a troubled physician-patient relationship, poor cognition, and patients not understanding the importance and need for the treatment. Therefore, interventions capable of preventing non-adherence and of maintaining treatment adherence are crucial in the care of people undergoing transplantations.

There are several methods to identify patients at risk for abandoning treatment. However, interventions to improve adherence are scarce. Bleser et al performed a systematic review with the purpose of analyzing the most effective interventions for improving adherence to immunosuppressive treatment after transplantation, and concluded that none of the interventions alone were superior in improving adherence, and, as other authors before them, they highlighted that more studies are needed in order to identify interventions with greater effectiveness.

Better transplant outcomes, including for heart transplants, were observed after immunosuppressive treatment, mainly when combined in the so-called triple therapy, which involves the association of corticosteroids, calcineurin inhibitor and antiproliferative agents. Recently, some institutions have recommended the inclusion of proliferation signal inhibitors (PSI). Furthermore, non-pharmacological measures regarding diet plans are highlighted, which aim at reducing the rates of metabolic syndrome and vascular disease of the graft, which is related to function loss, in addition to engaging in physical exercise.
Cardiac transplantation, which has improved significantly due to the development of new surgical techniques and new immunosuppressive drugs, represents the best treatment for patients with refractory heart failure (HF), although clinical treatment has improved the life expectancy in this patient group.\textsuperscript{11} By performing a careful assessment and selection of both the receiver and donor, it is possible to increase the survival rates, as well as the patients’ ability to engage in physical exercise, which increases their chances of being able to return to work and improves their quality of life.\textsuperscript{9,17-19}

At the Dante Pazzanese Cardiology Institute, a hospital specialized in the treatment of people with cardiovascular disease in São Paulo, Brazil, a heart transplant program has been active since 1991, with a total of 357 transplants performed by 2010, in which the one-year, five-year, and seven-year survival rates are 72.7\%, 61.5\%, and 56.4\%, respectively.\textsuperscript{15} The OPTN (\textsuperscript{3}) has reported that one-year, five-year and ten-year survival rates can reach 88.6\%, 73.1\%, and 53\%, respectively.

Among the complications that occur after heart transplantation, the most common is graft vascular disease, which accounts for a significant number of the deaths after the first year.\textsuperscript{17} Classic risk factors such as dyslipidemia, smoking, diabetes, and a sedentary lifestyle contribute to the onset of the disease.\textsuperscript{17} Another significant cause of mortality, mainly in the first 30 days after the transplant, is acute graft dysfunction.\textsuperscript{17}

A successful transplantation procedure is not based exclusively on the patients’ survival, but also on the possibility of achieving improvements in their physical capability, with an unquestionable improvement in their quality of life. Within this context, treatment adherence is fundamental and nurses play a crucial role regarding the self-care of transplant patients.\textsuperscript{6,17,19}

Dew et al\textsuperscript{20} conducted a study to verify if treatment adherence levels of lung recipients differ from that of recipients of other organs, particularly heart transplant patients, and concluded that the non-adherence rates regarding the use of immunosuppressant agents are significantly smaller among lung recipients (13\%) compared to heart transplant patients (21\%). This was also observed for the non-adherence to diet plans (34\% versus 56\%) and to quit smoking (1\% versus 8\%). The authors also found that poor support to caregivers, associated to the fact that they had one health plan increased the risk of non-adherence in both groups.

O’Grady et al\textsuperscript{21} identified factors specific to the patient (beliefs, education, loss of interest, economical aspects, psychological factors, life style, etc) and factors related to the treatment (complexity of doses, polypharmacy, side effects) as responsible for determining non-adherence to treatment.

It is crucial to know the impact of interventions to assure treatment adherence after a transplant, because it may determine the success of what may be the only treatment option for patients with refractory heart failure.

A search was performed to identify the existence of any systematic reviews regarding treatment adherence in heart transplant patients. This search was performed on PubMed, CINAHL, the JBI Library of Systematic Reviews, JBI CONNECT+, DARE and PROSPERO databases and yielded only one review addressing treatment adherence in heart or lung transplant patients\textsuperscript{22}, and three addressing treatment adherence in other organs transplant recipients alone or including primary studies with heart transplant patients.\textsuperscript{11-13}
The objective of one review was to estimate the prevalence of non-adherence with post-transplantation medication in heart or lung recipients, and to assess its clinical impact. The frequencies of non-adherence ranged between 1% and 42.9% for all drugs (immunosuppressant treatments and non-immunosuppressant treatments), and non-adherent recipients tend to experience worse outcomes compared to adherent recipients.

Other review addressed the factors involved in the abandonment of medical treatment after kidney transplantation, with the authors concluding that the highest risk of abandonment appears to be associated with being younger, female, unmarried, receiver of an organ from a live donor and having the transplant for a longer period of time.

The need for appropriate instruments to assess the risk of non-adherence to treatment after transplant motivated another systematic review. In the review, the authors included data regarding 20 instruments used to assess non-adherence in chronically ill patients that could be administered to transplant patients as well.

In another review, the interest was to analyze studies that had tested interventions with the objective of reinforcing the adherence to immunosuppressive treatment in patients who underwent solid organ transplants. Twelve studies were analyzed (seven studies on kidney transplant, three studies on liver, and two studies on heart and heart-lung transplants); most authors used pill count and serum dosage of pharmacological agents to assess adherence. Regarding the definition of non-adherence, some of the identified criteria were taking at least 80% of the prescribed medications, and consuming 98% of one or more drugs in a 3-month period. The interventions tested had a broad content: educational / cognitive (advice given by pharmacists using calendars, fliers), behavioral (the nurse revised the medication records with the patient) and studies that used mixed interventions. The authors concluded that no single intervention proved to be superior at increasing medication-adherence in organ transplantation, but a combination of interventions in a team approach for the chronic disease management of organ transplant patients may be effective in a long-term perspective. In this review, the most effective combination of interventions to enhance adherence was not found.

The present review protocol differs from the quoted ones in that it will focus: a) only on heart or heart-lung transplantation, and b) on adherence to pharmacological or non-pharmacological interventions. This project is also valid because the most similar review was accepted to be published in 2008. As the management of adherence to treatment is an important correlate for the success of heart or heart-lung transplantation, primary studies in this topic may have been published after 2008.

It is reasonable to admit that heart transplant patients may respond differently to adherence compared to recipients of other organs because of the meaning that is assigned to the heart. Besides representing a new chance of living, a perspective of a better future, a chance to rediscover the meaning of life, the awareness that there is no other treatment option, such as hemodialysis for kidney transplant, may predispose patients to different behaviors, including treatment adherence.

Thus, the research question is: in heart transplant patients, what interventions are more efficacious to manage adherence to the pharmacological and non-pharmacological treatment?
Keywords
patient compliance; psychology; health education; patient satisfaction; heart transplantation; organ transplantation; medication adherence; nursing assessment; nursing; monitoring; ambulatory; immunosuppressive agents; administration; therapeutic use; treatment outcome

Inclusion criteria

Types of participants
The review will consider patients, 18 years of age or older, regardless of gender, ethnicity, comorbidities, or other treatments, with heart or heart-lung transplantation receiving specific pharmacological and non-pharmacological treatments.

Types of intervention(s)

The review will consider interventions for managing treatment adherence of heart transplant patients. We will consider any intervention tailored and applied to maintain heart transplant patients using the prescribed pharmacological and non-pharmacological treatment. Examples of such intervention are: a) measures to prepare a patient to safely take prescribed medications/regimens and monitor for their effects (Medication Administration\textsuperscript{24}, or Medication Management\textsuperscript{24}); b) measures to “promote behavior acquisition/change” (Behavior Modification\textsuperscript{24}); c) measures to provide “instructions and learning experiences to facilitate voluntary adaptation of behavior conducive to health in individuals, families, or groups” (Health Education\textsuperscript{24}); d) measures to reinforce “self-directed change initiated by the patient to achieve personally important goals” (Self-Modification Assistance\textsuperscript{24}); e) measures to encourage “a patient to assume more responsibility for own behavior” (Self-Responsibility Facilitation\textsuperscript{24}); and f) measures to provide “the necessary information, advocacy, and support to facilitate primary patient care by someone other than a health care professional” (Caregiver Support\textsuperscript{24}).

Comparator(s)

Foreseen comparisons of intervention trials include those between any interventions applied to maintain heart transplant patients using the prescribed pharmacological and non-pharmacological treatment versus standard or routine care, or no additional care.

Types of outcomes

The review will consider studies that assessed, objectively or by self-report using validated instruments, patient adherence to pharmacological or non-pharmacological treatment.

For this systematic review, patient adherence to pharmacological or non-pharmacological treatment is defined as the extent to which a person's behavior – taking the medication, following a diet plan and/or make changes to their life style, corresponds to the recommendations of a caregiver, regardless of any agreement about following the recommendation because authors do not usually consider this element defined by the WHO.\textsuperscript{9}

Objective assessment of patient adherence to pharmacological or non-pharmacological treatment refers to direct observation of behavior, electronic monitoring, or serum dosage of pharmacological agents.
Types of studies

Studies will be considered for inclusion in the review if they are any type of randomized controlled clinical trial; in their absence, non-randomized trials, cohort and case-control studies will be considered for inclusion.

Search strategy

The search strategy is designed to identify published and unpublished studies written in Portuguese, English or Spanish. An initial search has already been performed on PubMed and CINAHL using MeSH (Medical Subject Headings) terms combined as follows: “Patient Compliance”[Majr] OR "Guideline Adherence”[Majr] OR "Medication Adherence”[Majr] AND "Heart Transplantation”[Majr]. In this first stage, 33 articles were located in PubMed. In CINAHL, the strategy (MH “Heart Transplantation”) and (MH “Patient Compliance”) or (MH “Guideline Adherence”) or (MH "Medication Compliance") yielded 38 articles. In these citations, the following descriptors were identified: patient compliance / psychology, health education / methods, patient satisfaction, psychology / heart transplantation, psychology / organ transplantation, medication adherence / psychology, transplantation / psychology, nursing assessment, heart transplantation / nursing, monitoring / ambulatory, immunosuppressive agents / administration, immunosuppressive agents / therapeutic use and treatment / outcome.

A new search will now be performed using all the keywords and descriptors identified in the preliminary search. The following databases will be used in this phase:

Bandolier,
Clinical Evidence,
Cochrane Library,
CINAHL,
Banco de Teses da CAPES,
DARE
Dissertation Abstracts International/Digital Dissertations,
EMBASE,
LILACS,
MEDLINE/Pubmed,
PsycINFO,
PROSPERO
ScienceDirect,
SCOPUS,
Web of Science,
MicroMedex,
A reviewer will read the titles and abstracts of all the obtained citations in order to verify if they meet the inclusion criteria. A second reviewer will analyze those that, in the opinion of the first reviewer, did not meet the inclusion criteria. The contentious cases will be kept in the study for the next stage when the full-text of all articles will be retrieved.

The reference list of each article will be reviewed to search for additional studies.

**Assessment of methodological quality**

Two independent reviewers will assess the methodological quality of each study selected for retrieval before their final inclusion in the review using the standardized Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) Critical Appraisal Tools (Appendix I). Eventual differences of opinion between the two reviewers will be resolved through discussion or with a third reviewer.

**Data collection**

Quantitative data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

**Data synthesis**

Quantitative papers will, where possible be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard Chi-square and also explored using subgroup analyses based on the different study designs included in this review. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

**Conflicts of interest**

The authors declare no conflict of interest.

**Acknowledgements**

None.
References


Appendix I: MASTARI appraisal instruments

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer ___________________________ Date ___________________________

Author ___________________________ Year _______ Record Number _______

1. Was the assignment to treatment groups truly random?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
2. Were participants blinded to treatment allocation?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
3. Was allocation to treatment groups concealed from the allocator?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
4. Were the outcomes of people who withdrew described and included in the analysis?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
5. Were those assessing outcomes blind to the treatment allocation?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
6. Were the control and treatment groups comparable at entry?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
7. Were groups treated identically other than for the named interventions  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
8. Were outcomes measured in the same way for all groups?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
9. Were outcomes measured in a reliable way?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
10. Was appropriate statistical analysis used?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

_________________________________________________________________________

_________________________________________________________________________
# JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____________________________ Date _____________________________

Author _____________________________ Year _______ Record Number _______

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<th>Yes</th>
<th>No</th>
<th>Unclear</th>
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<td>1. Is sample representative of patients in the population as a whole?</td>
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<td>2. Are the patients at a similar point in the course of their condition/illness?</td>
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<td>3. Has bias been minimised in relation to selection of cases and of controls?</td>
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<td>4. Are confounding factors identified and strategies to deal with them stated?</td>
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<td>5. Are outcomes assessed using objective criteria?</td>
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<td>6. Was follow up carried out over a sufficient time period?</td>
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<td>7. Were the outcomes of people who withdrew described and included in the analysis?</td>
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Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

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Appendix II: MASTARI data extraction instrument

**JBI Data Extraction Form for Experimental / Observational Studies**

Reviewer ___________________ Date _____________________

Author ___________________ Year _____________________

Journal ___________________ Record Number _____________________

**Study Method**

- RCT □
- Quasi-RCT □
- Longitudinal □
- Retrospective □
- Observational □
- Other □

**Participants**

Setting

Population

**Sample size**

Group A ______________ Group B ______________

**Interventions**

Intervention A

Intervention B

**Authors Conclusions:**

________________________

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**Reviewers Conclusions:**

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### Study results

#### Dichotomous data

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#### Continuous data

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