

Factors Related to Non-Adherence and Abandonment of Pulmonary Tuberculosis Treatment

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Objective: To analyze the evidence available in the literature on factors related to non-adherence to directly observed treatment by patients with pulmonary tuberculosis. **Methods:** This is an integrative literature review. The search was conducted between August 2019 and May 2020, by accessing the MEDLINE, LILACS, BDNF, BINACIS, IBECs, PUBMED, SCOPUS, and WEB OF SCIENCE databases, as well as via the SCIELO virtual library, selecting articles published between 2009 and 2019. **Results:** From the 1664 pre-analyzed studies, 57 articles that met the research question were identified and selected. Following data extraction, non-adherence factors were stratified into five categories, namely: patient-related factors, socioeconomic aspects, factors related to treatment, factors related to healthcare providers/service, and knowledge aspects, which presented a correspondence of 49, 33, 41, 23, and 20 articles, respectively. **Conclusion:** This study enabled an analysis of the scientific evidence regarding factors related to non-adherence to directly observed treatment by patients with pulmonary tuberculosis. It is concluded that the multifaceted range of aspects associated with such a research issue can be synthesized into factors related to patients, socioeconomic aspects, factors concerning treatment, factors related to healthcare providers/service, and aspects inherent to knowledge.

Descriptors: Cooperation and adherence to treatment. Directly observed therapy. Pulmonary tuberculosis. Systematic reviews as a topic.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*, whose transmission occurs through the air when a person infected with the bacillus excretes it by speaking, coughing or sneezing^{1,2}. According to the 2018 report by the World Health Organization (WHO)³, TB is among the ten leading causes of death in the world, accounting for approximately 1.3 million deaths in 2017. The WHO also assesses that 30 countries, including Brazil, concentrate 87% of all cases in the world³.

The treatment for TB currently recommended is antibiotic-based, with an estimated duration of six months, which usually includes the use of four first-line drugs, namely: Rifampicin, isoniazid, pyrazinamide and ethambutol³. The DOTS (Directly Observed Treatment Short-course) strategy is recommended worldwide because it gua-

rantees better treatment results. If drug-taking is observed at least three times a week in the first phase and twice a week during the maintenance phase, the treatment in question can be considered directly observed. The recommended treatment, although very effective, is not adhered to by all patients^{4,5,6}. According to Brazil (2011)⁴, when the patient stops coming back for at least 30 consecutive days, it is considered abandonment of treatment.

The abandonment of treatment is a problem of great importance for TB control, since it has as consequences the persistence of the infectious agent, the increase in relapse rates as well as mortality, besides providing greater chance of developing strains of bacilli resistant to treatment and contributing to the maintenance of the chain of transmission⁷. Although the WHO recommends that, for disease control, the goal of a cure is equal to or greater than 85% and that

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the dropout rate is less than 5%, adherence rates do not exceed 40% in developing countries^{3,8}. In 2014, the treatment dropout rate in Brazil was 11.3%⁹. When considering different countries we have varying percentages of non-adherence, being 35% in South Africa¹⁰ and 25.3% in China¹¹.

In view of the above, the objective of this study was to analyze the evidence available in the literature on the factors related to non-adherence and/or abandonment of treatment directly observed by people with pulmonary tuberculosis. It is of great importance to know such factors in order to create strategies to increase therapeutic success.

METHOD

Type of Study

This study was an integrative literature review, conducted with the purpose of deepening the scientific/professional knowledge on the topic of interest. The integrative review is a scientific method whose purpose is to synthesize results obtained in studies on a given theme/issue, "in a systematic, ordered, and comprehensive manner"¹².

The study included the six steps of an integrative review, which according to Mendes, Silveira and Galvão (2008)¹³ are: 1) identification of the theme and definition of the research question; 2) establishment of criteria for inclusion and exclusion of studies/ literature search; 3) definition of information to be extracted from the selected studies/ categorization of studies; 4) assessment of the studies included; 5) interpretation of results; 6) presentation of the review/knowledge synthesis.

For the development of the research question, we used the PICO strategy, which stands for Patient, Intervention, Comparison and Outcomes (outcome). Although this strategy is more commonly used in systematic reviews focused on clinical research, the choice of PICO for this integrative review was due to the understanding that the four components addressed in it are fundamental elements of the research question in the context of Evidence-Based Practice (EBP)¹⁴. Thus, the following guiding question was obtained: What is the available evidence in the literature on factors related to

non-adherence to directly observed treatment by patients with pulmonary tuberculosis?

Inclusion criteria

Regarding the inclusion criteria, it was pre-established that the studies to be included should be original articles (primary studies), whose object of study was to address non-adherence to directly assisted treatment for pulmonary tuberculosis, published between 2009 and 2019, in Portuguese, English, and Spanish, in portals/libraries, and in national and international databases. As exclusion criteria, studies that did not address the research question, review articles, and studies that addressed treatments other than DOT were considered ineligible.

The literature search took place between the months of August 2019 and May 2020, by accessing the databases: MEDLINE, LILACS, BDE-NF (Database in Nursing), BINACIS (Argentinian National Bibliography in Health Sciences), IBECS (Spanish Bibliographic Index of Health Sciences), but which were consulted via the VHL Portal (Virtual Health Library), PUBMED, SCOPUS, and WEB OF SCIENCE, as well as the virtual library SCIELO (Scientific Electronic Library Online).

Descriptors

The controlled descriptors used in the search were: A= Treatment Adherence and Compliance/ Cumplimiento y Adherencia al Tratamiento/ Cooperation and Adherence to Treatment; B= Directly Observed Therapy/ Directly Observed Therapy; and C= Tuberculosis Pulmonary/ Tuberculosis Pulmonary/ Pulmonary Tuberculosis. The descriptors in Portuguese, English and Spanish were used for the databases consulted through the VHL Portal, according to the DECS dictionary, as well as the descriptors in English for queries to PUBMED, SCOPUS, and WEB OF SCIENCE, according to the MESH dictionary.

In the crossings between the controlled descriptors in the three languages of interest, the Boolean operator "AND" was used, following the combinations A x B, A x C, and B x C. Chart 1 shows the number of articles identified in each database as the first result of the search.

Chart 1. Number of articles primarily identified in the search strategy.

Junctions Descritores (DECS e MESH)	No. of articles identified in the databases (by descriptor language)		
	Portuguese	English	Spanish
A x B			
Cooperation and Adherence to Treatment X Directly Observed Therapy	BDENF (1) BINACIS (2) IBECS(0) LILACS (3) MEDLINE (33) SCIELO (3) SCOPUS (1)	BDENF (5) BINACIS (2) IBECS (5) LILACS (12) MEDLINE (320) PUBMED (474) SCIELO (3) SCOPUS (16) WEB OF SCIENCE (31)	BDENF(0) BINACIS(0) IBECS (1) LILACS(0) MEDLINE (2) SCIELO (0)
A x C			
Cooperation and Adherence to Treatment X Pulmonary Tuberculosis	BDENF(1) BINACIS (2) IBECS(0) LILACS (7) MEDLINE (56) SCIELO (1)	BDENF (5) BINACIS (2) IBECS (3) LILACS (19) MEDLINE (257) PUBMED (510) SCIELO (4) SCOPUS (4) WEB OF SCIENCE (37)	BDENF (1) BINACIS(0) IBECS (2) LILACS (4) MEDLINE (4) SCIELO (2)
B x C			
Directly Observed Therapy X Pulmonary Tuberculosis	BDENF (2) BINACIS (3) IBECS(0) LILACS (9) MEDLINE (172) SCIELO (1) SCOPUS (1)	BDENF (4) BINACIS (3) IBECS (3) LILACS (18) MEDLINE (391) PUBMED (449) SCOPUS (456) SCIELO (10) WEB OF SCIENCE (211)	BDENF (2) BINACIS (3) IBECS(0) LILACS (9) MEDLINE (172) SCIELO (1)

Source: the authors (2020)

Search results were saved and exported gradually in the different digital file formats/extensions available for each search, for subsequent import into Rayyan, a free online application/website useful to assist researchers in developing systematic reviews¹⁵.

The set of files imported into Rayyan totaled 3755 articles, including the repeated references from all consulted databases and possible cross-references performed. Of these, 872 records were automatically excluded by the application for being repeated articles from the same database, resulting in 2881 articles. In addition, two articles were not found by Rayyan for having a different format from the ones accepted by the program. Of these, 1997 were considered by Rayyan as duplicates and 884 records as non-duplicates. The

researchers' attention was required to promptly solve each situation of apparent or real duplicity. Thus, following manual and automatic exclusions, 1217 articles were discarded, resulting in a set of 1664 articles pre-selected for review (Figure 1).

Evidence analysis

Then, the research advisor assigned the blind assessment function to three authors using the "Blind on" feature available in Rayyan, a triggering moment for the evaluation of the title and abstract of the 1664 pre-selected articles. After the evaluation of the inclusion or non-inclusion of the articles in the review, it was possible to identify divergence in 8.71% of the decisions. These

conflicts were resolved with the discontinuation of the initial blinding, with the joint reevaluation of the 145 articles with a heterogeneous initial evaluation, and with the final consensus on the inclusion/exclusion of the reviewed articles. At the end of the process, the reviewers considered that 1583 papers did not contain elements that would address this study's guiding question, and that another 24 papers did not meet the pre-selected criteria of the year of publication and languages, and a set of 57 papers were included in the review.

For the definition of the information to be extracted from the studies, an adapted version of the Ursi (2005)¹⁶ which included characteristics related to: identification, institution where the study was carried out, type of scientific journal, methodological characteristics of the study, assessment of methodological rigor. For the analysis and subsequent synthesis of the articles included, a summary table was used, also inspired by the Ursi (2005)¹⁶, which contained the following fields for completion: title of the article, authors, name of the journal, year of publication, host institution/study setting, results (factors related to non-adherence to DOT and factors related to abandonment of DOT), and conclusion.

Subsequently, keeping the alignment with the steps described by Mendes, Silveira, and Galvão (2008)¹³, the evaluation of the included studies was carried out. As part of the critical analysis of the articles regarding the quality of evidence, the classification of Stillwell et al. (2010)¹⁷ was used, which addresses seven levels of evidence.

After the evaluation of the studies, we proceeded to the interpretation of the results and presentation of the review/synthesis of knowledge. To this end, the articles were thoroughly read, using Minayo's thematic analysis technique (2010)¹⁸ to categorize the factors of dropout and non-adherence to DOT, as presented below.

RESULTS

Considering the 57 articles selected, 2017 was the year that presented the highest number of publications on this theme in relation to the others researched, with a total of ten published

articles. The International Journal of Tuberculosis and Lung Disease, in turn, was the journal that showed the highest number of publications on the subject in the period analyzed. The results of the search and the article selection process are summarized in the following flowchart.

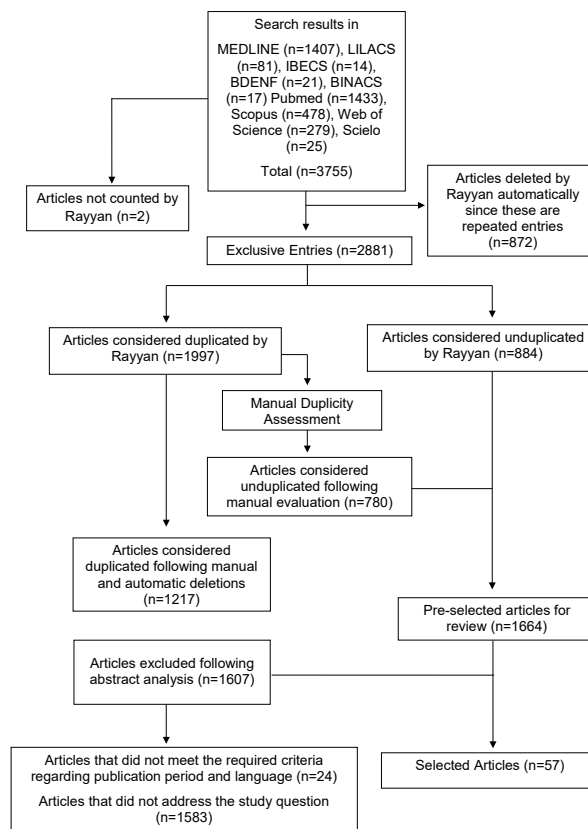


Figure 1. Flowchart of the study search.

Source: the authors (2020)

According to the level of evidence, one article was included in category II (randomized controlled trial); 45 were classified as IV (case-control or cohort study) and 11 as VI (qualitative or descriptive study). In this context, it is noticeable that most articles were found in level IV of evidence, that is, articles with analytical observational methodology and non-experimental. A significant portion of these articles referred to quantitative studies in which data collection through surveys administered to patients diagnosed with tuberculosis and to healthcare providers was favored.

For better visualization and understanding of the non-adherence/withdrawal factors found in the literature, we chose to group them into five

categories, according to the analysis of their contents. Taken together, the non-adherence/withdrawal factors were: patient-related factors, socioeconomic aspects, treatment-related factors, professional/service-related factors, and knowledge aspects.

The non-adherence factors related to patients were the following: Alcoholism, smoking, HIV co-infection, and beliefs (not feeling sick), present in 49 articles - 85.96% of the studies. Regarding socioeconomic aspects, addressed in 33 studies (57.89%), the factors identified were the following: Low level of education, treatment costs (medication and travel), low socioeconomic level, unemployment or informal employment, malnutrition, illiteracy, and housing with poor infrastructure. Regarding the factors related to treatment, addressed in 41 articles (71.92%), the following were registered: Stigma, logistics, re-treatment, and duration/adverse effects of DOT. Regarding factors related to healthcare providers and the service, the following emerged: Difficulties in the interaction between provider and patient, lack of structure, and lack of preparation (according to 23 articles - 40.35% of the studies). Finally, the knowledge aspects (present in 35% of the articles - 20 works) were lack of knowledge concerning the disease and lack of knowledge concerning the treatment. This set of findings is discussed below.

DISCUSSION

Patient-related factors

This category was the most found in the analyzed articles¹⁹⁻⁶⁷. Alcoholism, smoking, and HIV co-infection were the most frequently mentioned dropout factors. Other factors included older age, being male, and having hindering beliefs (patients feeling that they are no longer sick).

Divergences are observed with regard to gender, ethnicity, and age group. Although all the articles analyzed these factors, only six of them considered gender as a dropout factor, which in all of them was higher in males^{27,29,33,43,59,63}. Only two articles considered black and yellow ethnicity as non-adherence factors^{57,59}. Only eight studies

concluded that the age range was related to treatment abandonment, however, there was no consensus regarding the ages, since in one of them the age was over 15 years³⁴, two of them related non-adherence to the 20 to 39 age group^{42,59}, two other articles stated that being young was a factor in non-adherence^{38,39}, in one of the articles it was related to advanced age³¹, in another, it was higher in patients younger than 35 years⁶⁵ and, finally, one article pointed out the age group of 20 to 29 years as the one related to treatment abandonment⁵⁷.

A study in India from the World Journal of Pharmaceutical Research found no statistically significant results for variables such as gender, age, marital status, and residence⁶⁸, in agreement with the other 37 articles in this category^{19-26,28,30,32,34-37,40,41,44-56,58,60-62,64,66,67}.

Regarding the alcoholism issue, smoking and HIV co-infection, the majority^{20,22,24-31,37-40,42,43,46-48,51,53,55,57-62,64,65} of the articles that analyzed these variables concluded that they are factors related to treatment abandonment. These findings are consistent with those seen in other, more recent literature⁶⁹⁻⁷¹.

Socioeconomic Aspects

The socioeconomic aspects most commonly found concern low levels of education, expenses with treatment, which include medication costs and/or travel costs to the treatment center, and low socioeconomic status. Other aspects mentioned are related to being unemployed or having informal employment, malnutrition, and illiteracy.

In all articles where the socioeconomic issue was studied^{20,21,24,25,27,28,30,32,34,37,40-44,49-53,55-57,59-62,65,67,72-75}, The low socioeconomic level was pointed out as the cause. Other very important factors that lead to dropping out, also frequently mentioned^{20,21,24,27,28,32,37,40-44,50-52,55,57,59-62,65,67,72,73,75}, are low education, unemployment, low monthly income, and expenses with treatment. These expenses range from the purchase of medication, varying according to the country where the treatment is taking place, to the cost of travel to the health centers. Since these are months of

treatment, low income and unemployment become relevant issues that deserve to be highlighted among the factors of non-adherence. These factors are in accordance with what has been found in the literature^{68,71}.

Among the most current studies, there is one carried out in Brazil that addresses the social issue in TB treatment with a qualitative analysis based on the experience of health professionals. This research shows the association between TB and social vulnerability, such as the use of alcohol and illicit drugs, low income, and difficulty in commuting to health care facilities, factors that are consistent with those found in the results presented here. In addition, the research reinforces the positive influence of programs such as the Family Grant and the provision of transportation vouchers to assist in treatment adherence⁷⁶.

In a study conducted in Brazil and published in 2019⁷⁷, two groups of people were analyzed, both with TB: one of them received financial aid from the government, while the other did not. This study concluded that the government-assisted group experienced an 8% higher recovery rate than the other group.

Treatment-Related Factors

In this category the following factors stood out: stigma, logistics, retreatment, duration of treatment, and adverse effects. Among the adverse effects, the most prevalent are arthralgia and gastrointestinal ones, such as nausea, vomiting and epigastralgia, which leads many patients to abandon the treatment of the disease. The question of duration is also a factor of great influence in non-adherence, since treatment usually lasts six months. Regarding patients previously treated for tuberculosis, it was found that most of them did not undergo retreatment.

An important factor that was highlighted by the articles that fell into this category^{19-21, 23-25, 28-30, 33-38, 40, 41, 43-46, 48, 49, 51, 52, 54-56, 60-66, 72-74, 78-80} is the logistics. Several patients abandon treatment due to the long distance between their homes and the health center. Since health services are usually centralized, patients living in more distant regions, at a distance of 10 or more kilometers from

the centers, tend to abandon treatment. This issue is well elucidated in the literature and is in agreement with what was found in this study^{6,71}.

In a Brazilian article, it was observed that the decentralization of centers for primary care, involving the Family Health Strategy (FHS), in the city of Curitiba, Paraná, resulted in an increase in the number of people treated and a reduction in the proportion of dropouts. This article also highlights the importance of the FHS as the gateway to the health system and its fundamental role in patient reception⁸¹.

The issue of stigma deserves to be highlighted, because in all articles where this variable was analyzed^{20, 21, 30, 32, 35, 36, 43, 54-56, 66}, it was framed as a factor of non-adherence. The existing stigma in relation to the disease is a reason for shame for the patient, who often tries to hide the disease from the rest of the community, and, because of this, ends up not treating it. Many patients report fear of losing friends and family because of the stigma attached to the disease and the conditions that permeate it. All these issues triggered by the stigma end up impacting considerably on the quality of life of these patients. It is therefore important to explain to the family members and to the patient himself about the disease and its treatment, so that he can receive family support and not abandon the treatment.

A study by Linhares and Paz (2020)⁸², conducted in Family Health Strategy (FHS) units in the city of Rio de Janeiro, concluded that, due to stigma, patients tend to undergo social isolation, depression, and loss of will to continue with treatment, which becomes very difficult for them to overcome these obstacles.

Professional and Service-Related Factors

As it was possible to identify in 23 of the 57 articles^{22,24,25-28,30,32,34,36,40,44,46,47,52,55,56,67,72-74,78,79}, the lack of training of some healthcare providers, along with the lack of structure of some services where treatment was offered, negatively impacted adherence to tuberculosis treatment, since patients did not feel welcome to undergo treatment until its completion. The impoliteness and

rudeness of some providers were also mentioned in some articles.

The poor relationship between healthcare providers and patients stands out in this category as a significant factor in non-adherence. A negative relationship implies a lack of trust from patients towards providers who are treating them. This mistrust is compounded by the fact that patients do not feel welcomed by such providers and believe that they are not receiving adequate attention and support. All these factors ultimately influence non-adherence, along with the lack of training on behalf of some providers and the lack of structure of certain health centers.

Watermeyer and Penn (2019)⁷³ conducted a qualitative study, which was carried out through interviews, in South Africa, that related non-adherence to treatment to the difficulty of access to health services, either due to the lack of infrastructure for satisfactory patient care or due to the distance that rendered access impossible, which is in agreement with the findings of the other studies analyzed in this research^{22,27,31,32,34,40,45,47,49,56,61,73,74,79}. In addition, the problems in the system have caused a lack of faith in the patients of this locality, which goes beyond the factors seen previously. This article also reinforces the need for a good relationship between health professionals and patients, with trust and respect, which would avoid abandonment.

A study carried out with 27 TB patients in Family Health Strategy (FHS) units in the municipality of Rio de Janeiro reached the conclusion that not adapting routines and schedules according to the patients' needs and the difficulties they face causes these professionals to withdraw. On the other hand, the interest and dedication of the professionals to restore the patients' health, showing concern for them, assist in the creation of bonds, which are important for treatment follow-up⁸².

Knowledge Related Factors

This category includes aspects related to the lack of knowledge concerning the disease itself (tuberculosis) and the DOT treatment, both from healthcare providers and infected patients.

In all articles where the issue of knowledge was addressed, it was emphasized that not having information about the disease and its treatment was an important factor in non-adherence^{19,23,28-30,32,34,36,37,40,48,50,54,61,65-67,72,74,79}. The lack of knowledge on the part of the professionals resulted in the patients' disbelief in the treatment offered. They lost confidence in the improvement/cure. Furthermore, the lack of knowledge on the part of the patients led to abandonment, because they did not know the importance of finishing the treatment properly and were not instructed to do so. Thus, many of them, when they felt improvement, didn't see the need to continue with the DOT.

In a study conducted in India, it was found that not knowing the cause of TB, how TB spreads, the symptoms of TB, and whether TB is curable were associated with non-adherence to treatment. In addition, not knowing the duration of treatment, the names and colors of the drugs are also factors related to dropout⁶⁹.

Regarding the limitations of this study, it should be noted that some of the articles found presented a small study population. In addition, more specific studies were included, where the non-adherence factors were not addressed comprehensively, focusing instead on aspects that were more characteristic of the population and region studied. Thus, the loco-regional characteristics of each country and continent where the studies were carried out should be considered. In an attempt to compensate for this limitation, studies from different locations were used to compare results.

Given the harm that non-treatment can cause, it is essential to develop policies directed at the groups of patients most susceptible to abandonment. Considering the logistics, it would be interesting to make the DOTS strategy available to other health centers or to create new centers, in order to decentralize treatment and improve the transportation of patients. It would also be interesting to create intervention policies aimed at improving social conditions by promoting housing and increasing access to healthcare services. It will also be relevant to invest in the training of healthcare providers, in order to increase their knowledge as well as their skills in therapeutic interaction.

CONCLUSION

This study has enabled the analysis of the evidence available in the literature on the factors related to non-adherence to directly observed treatment by patients with pulmonary tuberculosis. It is concluded that the multifaceted range of aspects associated with such a research issue can be synthesized into patient-related factors, socioeconomic aspects, treatment-related factors, healthcare providers/service-related factors, and knowledge aspects.

Non-adherence to tuberculosis treatment deserves attention due to the issues it can cause to patients, the health system, and society. Such behaviors can increase the proliferation of multi-drug-resistant bacteria and increase the number of patients affected, impacting the quality of life and the management of health resources. It is recommended to regularly review and redesign response strategies, especially those directed to the groups most prone to non-adherence to treatment.

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