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FACTORS ASSOCIATED WITH NON-ADHERENCE TO LEPROSY MULTIDRUG THERAPY: A REVIEW

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ABSTRACT

Leprosy is one of the oldest diseases that affect man. With the emergence of multidrug therapy, usually consisting of dapsone, clofazimine and rifampicin, there has been a significant decline in the prevalence of leprosy worldwide. However, developing countries such as Brazil have struggled to achieve the elimination goals proposed by the World Health Organization. According to the literature, late diagnosis and non-adherence to treatment have been associated with this failure. Regarding adherence, studies have found different factors associated with unsatisfactory completion of treatment, such as: socioeconomic issues; the health system and its staff; and conditions related to the disease itself, the patient and the duration of treatment. Given the plurality of findings, it is considered necessary that more systematic studies be conducted in this context, investigating not only sociodemographic, but also psychological and social aspects.

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INTRODUCTION

Despite treatment and cure, leprosy remains a serious public health problem, especially in developing countries (NORIEGA *et al.*, 2016). To reverse this situation, it is necessary that the diagnosis occurs preferably in the early stages of the disease and treatment must be satisfactorily completed (DE SOUZA *et al.*, 2018; GARIMA *et al.,* 2018; World Health Organization, 2017). However, achieving these goals is often a challenge.

Regarding the diagnosis, Lockwood and Suneetha (2005) point out that despite being relatively simple, it requires knowledge of the health professional to differentiate leprosy lesions from other diseases. In addition, the patients's knowledge about the initial symptoms of leprosy is essential for them to seek medical attention as soon as possible (RODINI *et al*., 2010).

As for treatment, prolonged duration and side effects of multidrug therapy (MDT) have been associated with poor adherence and unsatisfactory completion of treatment (LIRA *et al*., 2012). As an aggravating factor, we highlight the difficulty in identifying non-adherent behavior during treatment, which is mostly perceived in cases of default. In this regard, non-adherence to treatment remains a major challenge for overcoming diseases, especially in the context of chronic diseases, and affects not only the sick individual but the entire health system (CUTLER; EVERETT, 2010; GLOMBIEWSKI *et al*. 2012; JIMMY; JOSE, 2011; SILVA *et al*., 2011). Among its main consequences, the development of morbidities, mortality, clinical complications and disabilities, waste of public resources, worsening of quality of life, occurrence of drug resistance and adverse events can be highlighted (GLOMBIEWSKI *et al*. 2012; JIMMY; JOSE, 2011; SILVA *et al.,* 2011). As an aggravating factor, Pagès-Puigdemont *et al*. (2016) claim that about 50% of patients with chronic diseases do not use medication as prescribed by the health team. This fact is worrisome, especially in the context of infectious diseases such as leprosy, in which non-adherence to multidrug treatment significantly compromises the control of disease transmission. It is, therefore, a topic of relevance not only for clinical practice, but also for society. In this sense, the present study aims to contribute to the knowledge about this topic, by presenting a brief history of leprosy and the factors pointed by the literature as associated with non-adherence to MDT, an essential factor for overcoming this disease.

MATERIALS AND METHODS

This article is a narrative review of the literature. In order to select the articles, a survey was conducted in the Pubmed and Scielo databases. For this, the following MeSH descriptors "Leprosy", "Treatment Adherence and Compliance", "Patient Compliance" and "Medication Adherence" were used. Original articles, review articles, and letters to editors were included, totaling 52 studies. The articles were fullyread in order to categorize them and then conduct their critical analysis.

DISCUSSION

Leprosy - Brief History

Present in much of religious literature, such as the Bible, Puranas (books depicting Hindu mythology) and Islamic medical books (HANUMANTHAYYA *et al*., 2017), leprosy is one of the oldest diseases that affect man (EIDT, 2004). According to Hanumanthayya *et al*. (2017), an Egyptian papyrus dating from 1550 BC already mentioned a disease that many scholars believe to be leprosy. However, it is only in 150 AD that the disease begins to gain more notoriety (OPROMOLLA, 1981). In 583 AD, the Council of the Catholic Church in Lyon (France) has determined the prophylactic rules regarding leprosy, with the isolation of the sick being the main one (EIDT, 2004). Thus, before the discovery of its treatment and cure, the main measure of leprosy control was the compulsory isolation of patients in places called leprosarium and leper colony (CABRAL, 2013; EIDT, 2004). Despite being a way to prevent transmission, this measure ended up violating human rights, and had little contribution to the advancement and improvement of treatment (MATTOS; FORNAZARI, 2005).

From the 1940s, with the promising results of sulfone use, there were improvements in leprosy treatment, leading to discussions on the need for patient isolation (EIDT, 2004; OPROMOLLA; LAURENTI, 2011). Subsequently, at the 7th International Leprosy Congress held in Tokyo in 1958, it was defined that isolation had little or no positive influence on treatment, prioritizing medication as a prophylactic measure (OPROMOLLA; LAURENTI, 2011). In Brazil, the end of compulsory isolation occurred legally in 1962, due to federal decree 968/1962 (MACIEL, 2003), but there are reports of these practices until the late 1980s. With the increasing number of reports of drug resistance after monotherapy regimen, in 1981 the World Health Organization (WHO) began to recommend the multidrug therapy (MDT), used worldwide until today (WHO, 2016). To better conduct drug treatment, the operational classification of the disease was developed, which must be specified at the time of diagnosis. In cases where there are few skin lesions (up to five) and insufficient number of transmission bacilli, the disease is called paucibacillary - PB. The multibacillary type - MB - is the most severe form of the disease, with higher concentration of bacilli and lesions (six or more), and consequently a high degree of contagiousness (BRASIL, 2017; BRITTON; LOCKWOOD, 2004). In addition to the operational classification of the disease, the classification of its clinical form is also employed. The most commonly used in Brazil are Madrid, proposed in 1953, in which leprosy is classified as undetermined , tuberculoid , borderline and lepromatous, and Ridley & Jopling, 1966, used the terminologies tuberculoid form (TT), borderline tuberculoid (BT), borderline borderline (BB), borderline lepromatous (BL) and lepromatous (LL) (LASTÓRIA; ABREU, 2012). The treatment regimen varies according to this classification, being the standard MDT regimen for PB cases consisting of Rifampicin and Dapsone (sulfone), with an average duration of six months, whereas for MB by Dapsone (sulfone), Rifampicin and Clofazimine, with an average duration of twelve months (GOULART *et al*., 2002; BRAZIL, 2017).In order to complete the treatment, the patient must attend the health service monthly to take the supervised dose of medication (600 mg rifampicin + 100 mg dapsone to PB patients and 600mg rifampicin + 100 mg dapsone + 300 mg clofazimine to MB patients) and take the blister of MDT for a self-administered daily dose (100 mg dapsone to PB patients and 100 mg dapsone + 50 mg clofazimine to MB patients) (GONÇALVES *et al*., 2019). In cases of allergies or complications due to any of these drugs, the alternative treatment regimen is prescribed, with the prescription of Minocycline and / or Ofloxacin (URA *et al*., 2007). In addition, according to the body's response to the drug, the medical team may choose to extend the treatment to avoid insufficient treatment. It is important to highlight that with the use of MDT, the disease is not only combated individually, but also acts in the chain of transmission, since in treatment the individual stops transmitting the disease (RAFFERTY, 2005).

Assessment of adherence to drug treatment: inherent challenges

The concept of treatment adherence may vary from the perspective of health professionals. However, it can be considered as adhered the patient who follows the agreed with the healthcare team, by using at least 80% of the prescribed treatments, paying attention to doses, schedules, etc. (LEITE; VASCONCELLOS, 2003; BEN, NEUMANN; MENGUE, 2012). As for its evaluation, there is no consensus on which method could be considered "gold standard" (WILLIAMS *et al*., 2013), making the task of measuring it complex. In addition, the challenge is also faced by those who seek to develop and validate new assessment techniques and/or instruments, since there is generally low agreement between the methods. This is mainly due to the fact that each one evaluates different dimensions of the same construct (SANTA HELENA; NEMES; ELUF-NETO, 2008). For these reasons, different methods, whether direct or indirect, have been employed by researchers and health professionals to assess treatment adherence (DEWULF *et al*., 2006). Direct methods are those using biological fluids (blood, urine, etc.) to detect the presence of the drug in the patient's body (OBRELI-NETO *et al.,* 2012). Indirect methods, usually the most commonly used, are those in which information about the drug regimen is obtained by applying structured questionnaires, pill counts, follow-up of medical records, use of the Medication Event Monitoring System (MEMS), etc. (OBRELI-NETO *et al.,* 2012). According to Obreli-Neto *et al*. (2012), both methods have limitations. In the case of direct methods the main limitation is the high financial cost, the discomfort generated in the patient (for fluid sample collection), and that it would only portray the recent use of the medication, being subject to patient manipulation. In the case of indirect, the researcher or health professional is subject to the patient omitting or changing important information, not having a consolidated instrument capable of measuring adherence in different types of disease, absence of information in medical records, etc. (BEN; NEUMANN; MENGUE, 2012; OBRELI-NETO *et al.*, 2012). Regarding leprosy, one of the most used criteria to identify irregular conduct in the treatment of MDT is the lack of assistance to the healthcare service for taking the dose and withdrawing medication (WEIAND; THOULASS; SMITH, 2012). When the maximum allowed treatment time is reached, which would be nine months for PB cases and eighteen months for MB cases (BRAZIL, 2017), and the recommended treatment has not been completed, the case is considered treatment default. This control is usually made from the patient's absence to the medical appointments, reported in his medical record (BRAZIL, 2017).

Factors associated with non-adherence to leprosy multidrug therapy

In a Brazilian study conducted in Fortaleza (State of Ceará, Brazil), Lira *et al.* (2012) interviewed 70 leprosy patients in order to assess the degree of adherence and its possible barriers. The authors stated that of these, 62.9% had low adherence according to the Morisky Green Test (MGT), despite reporting being aware of the risks associated with the disease. The main complaints identified by the authors regarding treatment were its prolonged duration and reactions triggered by it. Similar results were found by Kumar *et al.* (2015), who state that the main motivation for treatment default identified in their sample (n=363) refers to the adverse effects caused by MDT, such as weakness, vomiting, diarrhea, among others. In addition, the authors found that the highest dropout rate occurred at the beginning of treatment, an aspect also reported by Rao (2008). In this regard, Chalise (2005) points out that several studies have maintained that poor knowledge about the disease and its treatment, together with unfavorable socioeconomic factors, would be associated with not properly attending to what was prescribed by the health team. These data highlight the need for the reception and dissemination of knowledge about the disease and its possible complications by the health team, especially in the early stages of treatment, when the individual is still unaware of their condition. In the context of leprosy, this becomes a challenge, especially because, as noted by the author, most individuals not adhering to MDT were illiterate, hard-working and from lower economic classes, characteristics highly associated with neglected diseases.

Raju, John and Kuipers (2015), on other hand, identified by analyzing the perspective of 895 respondents, of which 320 were people affected by leprosy, that seeing or not seeing improvements in the symptoms may lead to non-completion of MDT. Other factors associated with this problem were the fear of being seen at the treatment centre, lack of companion for medical consultation, lack of perception of family support, lack of perception of community support, work commitments, cost of travel to the treatment centre, being “labeled” as a person with leprosy, lack of transport, comorbidities, among others, similar data to those found by Coebergh and Buddingh (2004). Similarly, Nwosu and Nwosu (2002) state that attendance at meetings, work at home, fear / shame / indignation and lack of confidence in treatment were significantly associated with patient absenteeism in their sample (n=53). Raju *et al.* (2016) by analising 3.579 new cases of leprosy identified a statistically significant difference between the groups classified as multi or paucibacillary in relation to treatment adherence, where the MB is less adherent than PB (p = 0.04). Similarly, when distributing the irregular patients in his sample (n=6.291), Rao (2008) observed the largest irregularity among the multibacillary cases, but without statistical significance. This is a matter of concern, since untreated multibacillary cases are mainly responsible for maintaining disease transmission (CRESPO; GONÇALVES; PADOVANI, 2014). In addition to the operational classification, Raju *et al.* (2016) stated that gender is also correlated with treatment adherence (p = 0.04), with a lower degree of adherence in male patients. Contrary to this Kumar *et al.* (2004), when investigating data from 273 patients, also identified significant associations between gender and treatment completion, but the lowest degree of adherence was found in females. In addition to gender, Kumar *et al.* (2004) also found significant associations of adherence with educational level and disability grade 0 and I, being the last one also cited by Orozco Vargas *et al.* (2013). Other than that, Luna *et al.* (2010) performed a qualitative assessment with six non adherent patients with leprosy and stated that the difficulty in performing their daily activities and lack of comunication may be related to non adherence, while Trindade *et al*. (2009) observed that 54% of the 57 cases registered as default of MDT in the Notification Disease Information System - SINAN - referring to João Pessoa (State of Paraíba- Brazil) stated that the regular use of alcohol is the main cause of default. Heukelbach *et al*. (2011) identified in their sample (n = 806) that the main causes for interrupting treatment were the difficulty for swallowing pills, few rooms in the house, unavailability of MDT in health centers and change of residence. Heijnders (2004), in turn, identified by interviewing 76 people with leprosy that individuals from lower social classes tend to adhere less to treatment, whereas Chichava *et al*. (2011), as well as Heukelbach *et al*. (2011) stated that the most mentioned reason by patients for stopping treatment was the lack of medication in health centers. Thus, it is possible to state that most studies point to patient-specific characteristics as important factors for non-adherence. From this premise, the success or otherwise of treatment can be understood as the responsibility of the patient, with the health service and professionals in the background (REINERS, 2008). However, it is noteworthy that success in treatment becomes possible not only due to the patient's behavior, but also due to the good relationship with the health team, which must be based on understanding, respect and, above all, efficient communication.

Final Considerations

This study aimed to conduct a review of narrative literature on the factors associated with non-adherence and default to treatment in the context of leprosy. Given the above, it is possible to state that the main factors associated with non-adherence refer to socioeconomic issues, the health system, as well as conditions involving the disease itself, the patient and treatment. Regarding the variables investigated, most of the studies were based mainly on data that outline the participant's sociodemographic profile. It is likely that for this reason, added to the use of different methodologies, a plurality of variables has been related to this topic. Regarding the psychological and social aspects of the participants, an important factor in the context of chronic diseases and treatment adherence, little has been explored. When addressed, they are based on qualitative data, which may be more susceptible to bias. In contrast, psychological aspects related to leprosy disease are the subject of several studies (ARACHCHI *et al*., 2017; REIS *et al*., 2014; SILVEIRA *et al.,* 2014; TSUTSUMI *et al.,* 2007). However, analyzes are performed to trace the psychological profile of patients, their perception of stigma, quality of life, among others, without investigating the association of these factors with treatment adherence. However, the World Health Organization (2016) points to the importance of recognizing the social and human aspects that involve leprosy, as these also negatively interfere with timely diagnosis and treatment outcomes. Eidt (2004) reinforces this need by stating that people affected by leprosy *"suffers more moral than physically"* (p.7), a reflection of a long process of stigmatization, present since the first mention of the disease. In this sense, it is suggested that further studies be conducted on this theme in order to investigate the role of the psychological and social aspects of leprosy in adherence to multidrug therapy. Thus, new proposals for patient care can be formulated, thus contributing to the reduction of new cases of the disease.

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