What factors influence adherence and non-adherence to multi-drug therapy for the treatment of leprosy within the World Health Organisation South East Asia region? A systematic review


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What factors influence adherence and non-adherence to multi-drug therapy for the treatment of leprosy within the World Health Organisation South East Asia region?
A systematic review

Timothy Meadows\textsuperscript{a} & Gail Davey\textsuperscript{a}

\textsuperscript{a}Brighton and Sussex Medical School, BSMS Teaching Building, University of Sussex, Brighton, BN1 9PX, UK
ORCID: https://orcid.org/0000-0003-3333-3330

Submitted 27 July 2022; Accepted 20 October 2022

Summary

Introduction Leprosy is an infection caused by \textit{Mycobacterium leprae}. Despite curative treatment being available, leprosy is still prevalent worldwide, with little change in annual cases observed in the past decade. The WHO South East Asia region is the worst affected, accounting for over 70\% of new cases. One reason leprosy transmission still occurs is non-adherence to multi-drug therapy. This project aims to determine the factors that influence adherence.

Methods A systematic review was performed using 6 databases. This returned 402 unique results. Screening of the title and abstract resulted in 362 of these being excluded. From the remaining 40, full-text analysis identified 17 studies that met the inclusion criteria and formed the review. Both qualitative and quantitative methods of collecting and analyzing data were used to form a non-quantitative synthesis of the findings.

Results Four factors influenced adherence: medication-related, healthcare-related, patient-related and society-related. From these, lack of knowledge about leprosy and multi-drug therapy was a predominant barrier to adherence, which related to all of these factors. Stigma and being female were also seen as important barriers to adherence - these manifested in numerous ways.

Conclusion The review identified diverse barriers to adherence to MDT and no simple intervention will overcome these. Rather, wider issues such as continuous access to healthcare (particularly for women), stigma reduction and patient education need to be addressed. Improving these will increase patient confidence in, and access to, MDT, which will ultimately result in improved adherence to therapy.

Keywords: Leprosy, adherence, multidrug therapy

Correspondence to: Timothy Meadows, 20 Faraday Road, Ipswich, Suffolk, IP4 1PU, UK
(e-mail: timmeadows1991@gmail.com)
Introduction

Leprosy is a bacterial infection caused by *Mycobacterium leprae* and to a lesser extent *Mycobacterium lepromatosis*. The infection predominantly affects the skin and peripheral nervous system, although other organs such as eyes can also be affected.

The WHO recommends that leprosy be diagnosed based on clinical examination, with classification being based on the number of skin lesions present and the presence of acid fast bacilli on a skin-slit smear test. Leprosy is either classified as multibacillary (MB) or paucibacillary (PB). MB is defined as more than 5 lesions present or a positive skin-slit smear test. PB is defined as between 1 and 5 lesions present in addition to a negative skin-slit smear test. The treatment of leprosy is dependent on classification.

Multi-drug therapy (MDT) was first introduced in 1982 and has been available free of charge to patients since 1995. MDT began as a 2 or 3 drug combination, dependent on classification, but the most recent recommendation is that all patients receive all three drugs, for 6 months in the case of PB patients and 12 months for MB patients. Effectiveness has been shown through low relapse rates of 1.07% for PB and 0.77% for MB leprosy. MDT regimens are shown in Table 1.

Despite initial success of MDT, the number of new cases reported annually has plateaued. In 2019, there were 202,185 new cases of leprosy reported to the WHO, with similar figures having been reported since 2010. Although figures reported in 2020 were much lower, this was due to reduced case finding activities as a result of the SARS-COV2 pandemic. The number of cases disproportionately affects the WHO South-East Asia (SEARO) region, which accounts for approximately 70% of new cases year-on-year.

The lack of reduction in case numbers over the past 10 years indicates that transmission of the infection is ongoing. One reason for this is the inadequate treatment of leprosy through non-adherence and incomplete MDT. Completion of leprosy treatment is defined as completing 6 months of MDT for PB leprosy within 9 months, and completing 12 months of MDT for MB leprosy within 18 months. If patients do not complete therapy within this timeframe, they are considered non-adherent to MDT.

Official figures suggest high adherence rates in MDT within the SEARO region, with completion rates of 93.7% for MB leprosy and 96.1% for PB leprosy being reported. However, published literature suggests much higher rates of non-adherence to MDT within the region, with rates of over 50% being reported.

Non-adherence to MDT can result in consequences not only to the patient but also to the wider global community. For the patient, inadequate treatment means that *M. leprae* can still persist, even if symptoms have subsided. As a result, over time, the bacterial load of the patient will increase, resulting in reoccurrence of symptoms. The WHO reported that 15,733 patients globally were re-treated with MDT in 2019, adding that “in-depth analysis of retreatment to determine the reasons for discontinuing treatment would improve compliance.” Insufficient treatment can result in poor patient outcomes such as disabilities and deformities as a result of disease progression.

In the wider community, one consequence of non-adherence is antimicrobial resistance (AMR). Although levels of AMR in leprosy are low, emergence of rifampicin resistance has been reported, and is higher in relapsed infections. As rifampicin is the most bactericidal agent against leprosy, emerging resistance will result in an increased need to utilize less efficacious second-line agents and increased risk of treatment failure. There is also evidence to suggest a direct causative link between non-adherence to MDT and development of treatment-resistant leprosy.
Due to high rates of non-adherence to MDT and its consequences, it is important to identify why non-adherence occurs. The purpose of this review is to determine the factors that influence adherence or non-adherence to MDT. Knowing the barriers and enablers to adherence may help develop interventions to encourage adherence to MDT. The review will focus on the SEARO region. As this is the region with the greatest global burden, it will receive the most benefit from interruption of transmission that will result from improved adherence to MDT, amongst other interventions.

**Materials and methods**

**REGISTRATION**

Prior to the review commencing, it was registered with PROSPERO. The registration number for the review is CRD42021242092 and can be accessed at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=242092.

**AIMS AND OBJECTIVES**

The aim of this paper is to identify factors that are either barriers or facilitators for patients in the WHO SEARO region to adhere to WHO-recommended MDT. The following research questions will be discussed:

1. What are the barriers for patients with leprosy located in the WHO SEARO region to adhere to WHO recommended MDT?
2. What are the enablers for patients with leprosy located in the WHO SEARO region to adhere to WHO recommended MDT?

**DATABASES AND SEARCH STRATEGIES**

A review of the literature was conducted in June 2021. Databases used were Embase, Medline, Pubmed, PsychInfo, Global Health and InfoLep. These were selected based on their relevance to healthcare, global health and leprosy. Search strategies can be found in Appendix A. Based on the findings of an initial scoping of the literature, it was decided that searching the grey literature would provide limited additional benefit to the overall findings.

Identified citations and abstracts were exported to the citation management software Zotero. Once all citations were exported, duplicates of citations were removed. Publication titles and abstracts were screened and excluded from further review if at least one of the criteria for exclusion was met. Publications were excluded if a full copy could not be sourced. Once sourced, the full papers were reviewed to determine if they met the inclusion criteria. The research software Rayyan was used for this.

**INCLUSION CRITERIA**

1. Studies include leprosy patients, caregivers and/or healthcare workers
(2) Studies addressing adherence or non-adherence to MDT
(3) Studies conducted in a WHO SEARO member state
(4) Studies published in English
(5) Studies published between 1982 (when MDT first became available) and 2021
(6) Observational quantitative studies, qualitative studies and mixed methods studies

EXCLUSION CRITERIA

(1) Previous systematic reviews, commentaries of the literature and letters to the editor

RISK OF BIAS ASSESSMENT

A quality appraisal of included studies was performed to determine validity. For quantitative and qualitative studies, this was performed using the National Institute for Health and Care Excellence (NICE) Quality Appraisal checklists for quantitative studies and qualitative studies.\(^\text{15,16}\) For mixed methods studies, appraisal was performed using the Mixed Methods Assessment Tool.\(^\text{17}\)

DATA COLLECTION AND SYNTHESIS

The qualitative studies identified were thoroughly examined using line-by-line coding. Although software was considered for this, the number of studies identified meant that this process could be done manually to the required standard. Relevant data were extracted and added to a thematic analysis framework designed for the study. Through this framework, codes were identified and, from these, key themes were generated.

For quantitative studies, a data extraction tool was developed. Data collected were age and gender of leprosy patients, leprosy classification, disability grade, distance from healthcare services, socioeconomic status, occupation and level of education.

Once all the relevant data were extracted, a non-quantitative synthesis of the findings was performed. This integrated quantitative and qualitative data, whereby significant quantitative results were reported, and qualitative data provided explanatory insight to potential reasons why these results were observed.

Results

STUDY SELECTION

The literature review and study selection process is shown in Figure 1 using the PRISMA flow diagram template.

STUDY CHARACTERISTICS

In total, 17 studies were selected for review. Six were purely qualitative, 9 were pure quantitative and 2 were mixed methods studies. Regarding location, 6 were conducted in Nepal, 8 were conducted in India and 3 were conducted in Indonesia. A summary of the studies can be seen in Table 2. The summary of the quality appraisals for the studies can be found in Tables B.1–B.3.

One noticeable difference in the studies was definition of MDT adherence. Only 3 studies used the definition provided by WHO. In 3 studies set in Nepal, the duration of MDT for MB leprosy was 24 months, which corresponded with national guidelines at time of publication. Raju \textit{et al.} classed non-adherence as not completing the required number of doses of MDT, although no time frame in which therapy should be completed was specified. Rao provided a
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<th>Author and year</th>
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<th>Study setting</th>
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<th>Study aim</th>
<th>Definition of non-adherence</th>
<th>Factors identified for adherence or non-adherence for MDT</th>
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| Heijnders 2004¹⁸ | Qualitative: 1 to 1 interviews | Government health posts within the project area for Eastern Leprosy Control Project in Nepal | 67 MB leprosy patients (LPs) | To explore the experiences of people with leprosy at health care services and how this affects adherence to therapy | Patient missing more than 12 monthly clinic visits | Factors associated with negative impact on adherence:  
  ∙ Negative attitudes of HCWs to LPs from lower social classes  
  ∙ Lack of counselling on MDT, especially regarding ADRs  
  ∙ Poor implementation of proxy policy whereby family members inappropriately prohibited from collecting MDT for LPs  
  ∙ Strict time schedules whereby MDT can be collected  
 Factors associated with positive impact on adherence:  
  ∙ Positive attitudes of HCWs to LPs from higher social classes |
| Heijnders 2004¹⁹ | Qualitative: 1 to 1 interviews | Government health posts within the project area for Eastern Leprosy Control Project in Nepal | 67 MB LPs | To explore how patients’ understanding of their leprosy diagnosis and treatment affect their health seeking behaviour and adherence to therapy | Patient missing more than 12 monthly clinic visits | Factors associated with negative impact on adherence:  
  ∙ Patient belief that they do not have leprosy but rather a less severe skin disease  
  ∙ ADRs, particularly hyperpigmentation of skin due to clofazimine  
 Factors associated with positive impact on adherence:  
  ∙ Fear of worsening symptoms and subsequent stigma  
  ∙ Confidence in MDT |
| Susanto 2017²⁰ | Qualitative: focus groups | 2 self-care groups within the city of Jember, Indonesia | 17 LPs | To determine what effects attending a self-care group has on a patient’s perceived treatment of their leprosy | Not defined | Factors associated with negative impact on adherence:  
  ∙ Unrealistic expectations of MDT  
  ∙ Lack of confidence in MDT  
 Factors with positive impact on adherence:  
  ∙ Effective counselling for MDT |
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| Correia 2019\(^{21}\) | Qualitative: 1 to 1 interviews | 4 hospitals (including 2 leprosy referral hospitals) in Nepal | 11 LPs and 15 working in leprosy health services | To explore educational needs of patients with leprosy regarding their diagnosis and treatment | Not defined | Factors associated with negative impact on adherence:  
  • Long treatment duration  
  • Poor patient knowledge of leprosy  
  • Experiencing ADRs, particularly hyperpigmentation of skin due to clofazimine  
Factors associated with positive impact on adherence:  
  • Patient knowledge on consequences of untreated infection |
| Lal 2014\(^{22}\) | Qualitative: 1 to 1 interviews | West Bengal in India. (Precise settings not described) | 20 parents of children taking MDT (1 parent per child) | To explore the experiences of parents with respect to the diagnosis and treatment of leprosy in their children | Not defined | Factors associated with negative impact on adherence:  
  • Hyperpigmentation of skin due to clofazimine |
| Chalise 2005\(^{23}\) | Qualitative: 1 to 1 interviews | 2 primary health centres, 8 health posts and 1 district health office in Dhanusha district, Nepal | 57 LPs | To determine the socio-economic characteristics of leprosy patients who are non-compliant to MDT and to explore their knowledge about their disease and treatment. | MB leprosy: patient not completing 12 month MDT within 18 months  
PB leprosy: patient not completing 6 month MDT within 9 months | Factors associated with negative impact on adherence:  
  • Being a laborer or daily wage worker  
  • Belonging to a low socioeconomic class  
  • Unrealistic expectations of MDT  
  • Poor patient knowledge of leprosy and MDT |
Table 2. (Continued)

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| Heynders 2000²⁴ | Quantitative: case-control study | 1 sub-regional referral centre in Nepal | 1442 LPs | To examine potential risk factors for non-compliance to MDT. | MB leprosy: patient not completing 24 month MDT within 36 months PB leprosy: patient not completing 6 month MDT within 9 months | Factors associated with negative impact on adherence:  
  - Women from India with MB leprosy more likely to show non-adherence to MDT compared to Indian men with MB leprosy. |
| Raju 2015¹⁰ | Quantitative: case-control study | 4 leprosy hospitals in India | 3579 LPs | To explore correlations between rate of defaulting with demographic and disease-related variables. | Not defined | Factors associated with negative impact on adherence:  
  - Being male  
  - Having MB leprosy as opposed to PB leprosy |
| Mushtaq 2020²⁵ | Quantitative: case-control study | 1 tertiary care hospital in India | 743 LPs | To determine the magnitude of MDT default and whether these were associated with clinical or demographic variables. | Not defined | Factors associated with negative impact on adherence:  
  - Being a laborer  
  - Having MB leprosy as opposed to PB leprosy  
  - Living in the district where the hospital is based |
| Saraswat 2019¹² | Quantitative: single-group study | 2 tertiary care centres in India | 124 LPs | To identify reasons why patients defaulted from MDT and why they presented to restart MDT | Not defined | Factors associated with negative impact on adherence:  
  - Poor accessibility of health services  
  - Fear of stigma  
  - Experiencing ADRs  
  - Ill health  
  - Patient belief that MDT is unnecessary  
  - Loss of work hours |
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<tr>
<td>Rao 2008²⁶</td>
<td>Quantitative: cross-</td>
<td>6 leprosy hospitals in India</td>
<td>6,291 LPs</td>
<td>To identify demographic, clinical and social factors that result in non-adherence to MDT</td>
<td>Patient has not collected MDT for 3 consecutive months</td>
<td>Factors associated with negative impact on adherence:</td>
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<td>• Negative attitudes shown to LPs from HCWs</td>
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<td>• Poor accessibility of health services</td>
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<td>• Social stigma</td>
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<td>Susanti 2017²⁷</td>
<td>Quantitative: cross-</td>
<td>1 public health centre within the city of Jember, Indonesia</td>
<td>35 LPs</td>
<td>To assess perceived social stigma, adherence to medication and motivation for healing amongst leprosy patients</td>
<td>Not defined</td>
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<td>sectionnal analysis</td>
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<td>• Longer infection time before seeking healthcare services</td>
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<td>Kumar 2004²⁸</td>
<td>Quantitative: cross-</td>
<td>1 hospital, 5 primary health centres and 9 health posts in Dhanusa district, Nepal</td>
<td>580 LPs</td>
<td>To investigate gender differences in epidemiological factors associated with MDT completion status</td>
<td>MB leprosy: patient not completing 12 month MDT within 18 months</td>
<td>Factors associated with negative impact on adherence:</td>
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<td>sectionnal analysis</td>
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<td>PB leprosy: patient not completing 6 month MDT within 9 months</td>
<td>• Being female</td>
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<td>• Having grade 2 disabilities</td>
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<td>Hajid 2019²⁹</td>
<td>Quantitative: cross-</td>
<td>Gowa district in Indonesia (Precise settings not described)</td>
<td>100 LPs</td>
<td>To determine factors associated with medical compliance to MDT</td>
<td>Not defined</td>
<td>Factors associated with negative impact on adherence:</td>
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| Kumar 2015\(^{30}\) | Quantitative: cohort study | Agra district in India (Precise settings not described) | 1296 LPs | To assess treatment completion of leprosy therapy and identify reasons for defaulting for therapy | MB leprosy: patient not completing 12 month MDT within 18 months. PB leprosy: patient not completing 6 month MDT within 9 months | Factors associated with negative impact on adherence:  
- Being a woman with PB leprosy compared to a man with PB leprosy  
- ADRs (fever, malaise, GI effects, hyperpigmentation due to clofazimine)  
- Patient belief that they do not have leprosy  
- Patient belief that MDT is no longer necessary following improvement of symptoms |
| Raju 2015\(^{31}\) | Mixed methods with a sequential exploratory design. Study used focus groups followed by cross-sectional analysis | Key centres within 4 states in India | Focus groups: 13 focus groups (4 with LPs, 6 with village leaders and 3 with health workers), each with 8-12 participants. Cross-sectional analysis: 320 LPs, 302 heads of family and 273 community members | To explore factors that can influence adherence to MDT and to identify which of these factors are most important to leprosy patients, their head of family and other community members | Patient unable to complete the required number of doses of MDT as prescribed (no timeframe for which to complete MDT specified) | Factors associated with negative impact on adherence:  
- Having no support from family or wider community  
- Stigma of being seen going to clinic  
- Accessibility of health services due to cost or lack of transport  
- Negative attitudes shown to LPs from HCWs  
- Lack of understanding of when to attend health services  
- Unrealistic expectations of MDT  
- Patient belief that MDT is no longer necessary following improvement of symptoms  
- Greater accessibility to tradition therapies  
- Being a daily wage worker |
| Kar 2010\(^{32}\) | Mixed methods. Study used questionnaires and review of relevant literature (e.g. medical notes) | Kamrup district in Assam, India (Precise settings not described) | 254 LPs | To assess level of adherence to MDT and understand reasons for incompletion. | Not defined | Factors associated with negative impact on adherence:  
- Being female  
- Belonging to a socioeconomic class  
- Having a low literacy status  
- Poor accessibility of health services  
- Fear of stigma  
- Experiencing ADRs  
- Ill health  
- Lack of confidence in MDT |
different definition for non-adherence - patients missing 3 consecutive months of MDT. The remaining 9 studies did not provide a definition.
FACTORS AFFECTING ADHERENCE

The extracted data were analysed and 4 key overarching factors that affect adherence (both positive and negative) to MDT were identified.

1. Medication-related factors

One medication-related factor identified was the development of adverse drug reactions (ADRs) to MDT. From the quantitative data, discontinuation due to ADRs occurred in 9.6%–26% of patients.12,32 There appears to be a positive correlation between patient education on ADRs and adherence to MDT when they occur. Heijnders et al. found that no patients were counselled on ADRs and patients were surprised when these occurred, which resulted in some patients discontinuing MDT.18 In contrast, Susanto et al. found that patient counselling on ADRs and treating them when they occurred encouraged patients to continue therapy.20

One ADR of note is hyperpigmentation due to clofazimine, with one study stating that this led to discontinuation in 7.5% of MB leprosy patients.30 This was addressed in most qualitative studies.19,21,22 These found that hyperpigmentation due to clofazimine had a negative influence on adherence predominantly due to stigma and perceptions of beauty. In these settings, fair skin is perceived as more desirable, and development of darkened skin was very concerning to patients due to the associated social stigma. Lal et al. found that this stigma was the most common effect reported by parents of children with leprosy, and was manifested in their children being bullied in school.22 Not only did this result in non-adherence to MDT, but also absenteeism from school.

Another medication-related factor was patients not believing it necessary to complete the course due to symptom improvement. In one study, this was found to be the most important contributor to MDT non-adherence.31 Once again, ineffective counselling could have contributed to this. For example, Chalise et al. found the majority of patients did not know how long MDT should be taken for.23 Without this knowledge, patients may naturally believe that MDT is no longer needed when symptoms have resolved.

2. Healthcare-related factors

One healthcare-related factor identified was distance to services, which was reported in 4 quantitative studies.24–26,29 Interestingly, longer distances affected adherence both positively and negatively. From the 4 quantitative studies, 2 (Heynders et al. and Mushtaq et al.) found that longer distances were associated with greater adherence to MDT and the other 2 (Rao et al. and Hajid et al.) found that patients who had to travel further were more likely to be non-adherent to therapy.

One explanation is the rationale behind patients travelling long distances to access services. It is not uncommon for leprosy patients to travel to distant services for treatment in order to hide their status.24 Heynders et al. and Raju et al. found that attending local services was found to be associated with a fear of recognition and the increased risk of their leprosy status becoming known.18,31 Therefore, some patients decide to travel long distances to other services where they will not be recognized. The effort that these patients go to access these services is indicative of their motivation to obtain MDT, which is a strong facilitator for adherence. However, motivation alone is not sufficient in some cases to overcome barriers to accessing services, with geographic, financial and transport issues often cited as barriers to adherence.12,19,29,31,32

Another healthcare related factor was the provision of counselling provided to patients, which is related to health care worker (HCW) knowledge and the relationship between the
HCW and patients. Susanto et al. found that the benefits of adhering to MDT as well as treatment directions provided confidence to the patients to adhere to therapy. Inadequate counselling from HCWs presented as barriers to MDT adherence. Correia et al. found that poor knowledge and lack of training meant that HCWs were unable to address prevalent cultural and spiritual beliefs regarding leprosy. In addition Heijnders et al. also found that insufficient HCW knowledge of MDT resulted in inappropriate denial of MDT to some patients.

3. Patient-related factors

A number of key patient-related factors were identified, the most important being gender. Firstly, in studies that reported gender proportion, the majority included more men than women, with the proportion of women included in the studies ranging from 23% to 39%. The only exception is Kumar et al. where there was a more equal proportion of men and women included, due to participants being identified through active case finding.

Of the 8 quantitative studies that included gender as a variable for MDT completion, 4 found that women were statistically less likely to complete MDT than men, with Kumar et al. finding men were twice as likely to complete MDT than women. Three found no association between gender and MDT completion. Only 1 study (Raju et al.) found that men were more likely to default from treatment, although reasons for this were not explored.

One reason identified for women showing non-adherent behaviour was the practice of Purdah, whereby Hindu and Muslim women undergo a period of seclusion, with women needing to be accompanied when accessing healthcare. If no suitable person was able or willing to accompany the women, this presented a barrier to obtaining MDT. The lack of a companion was also observed in other studies as a reason for non-adherence. This signifies the difficulty some women have in accessing treatment in a patriarchal society. Kumar et al. also found that actual or perceived cost of transport was a barrier for women accessing treatment, alluding to the financial dependency that women have in patriarchal societies.

Another patient factor identified was patients’ understanding and beliefs about leprosy and MDT. Studies found that the patient’s definition of ‘cure’ was total resolution of symptoms and, in some cases, patients’ physical health returning to what is was prior to diagnosis. However, the physical symptoms of leprosy can be permanent or take a long time to heal, and adherence issues arise when patients are unaware of this. Not seeing improvement in signs and symptoms subsequently leads to patients losing patience and questioning the effectiveness of MDT. This concern was shared by one of the parents of a child with leprosy interviewed by Lal et al., who asked “my child has been taking treatment properly for a long time, then why has the patch remained white?” It is this loss in confidence in MDT that results in non-adherence in many cases.

A patient’s socioeconomic status also influenced adherence, with Kar et al. finding that 64.6% of patients who discontinued MDT were from the 2 lowest social classes of India, whereas 70.8% of patients who completed therapy where from the 2 highest social classes. Reasons include negative attitudes of HCWs to those of lower social classes and inability to afford transportation costs.

A further important contributor to this effect is patient occupation, particularly those who receive a daily wage (e.g. laborers). The loss of work hours in these patients were a reported factor for non-adherence in 7 studies. Due to the nature of daily wage working, patients are presented with a dilemma as to whether to attend the monthly clinic to collect MDT or to work. The loss of a day’s wages and the effect this could have on their livelihoods resulted
Adherence to MDT in South East Asia

...in patients deciding to choose work over attending clinics, particularly where long travel times were anticipated.21,31

4. Society-related factors

There were a couple of society-related factors identified that influenced adherence to MDT. One was family support provided to people with leprosy. It was found that the more positive support a patient had from their family, the more likely they were to adhere.20,29 Hajid et al. found that those who had strong support from family were far more likely to complete MDT.29 In contrast, other studies noted the lack of family support as a barrier to adherence.18,31 One reason why there may be a lack of support is the social harm that can come with having a person with leprosy in the family. This can result in family members discouraging patients from seeking healthcare locally, or forcing them to attend clinics further away.31 These factors contribute to problems with healthcare access that can result in MDT discontinuation, particularly in women.

The stigma of a leprosy diagnosis was often listed as a reason for discontinuing MDT, with Saraswat et al. and Kumar et al. listing stigma as the cause for MDT discontinuation in 25.8% and 18% of non-adherent participants.12,26,30,31 As observed, the issue of stigma is complex and can manifest in many different ways, including travelling further to access MDT and discontinuation of clofazimine due to hyperpigmentation. Interestingly, Heijnders found the fear of stigma positively influenced adherence of MDT, especially in those with mild symptoms.19 The fear of worsening symptoms, the risk of recognition of having leprosy and the associated social consequences were strong motivators in some cases to adhere to therapy.

Discussion

This review identified a relationship between lack of knowledge regarding leprosy and adherence to MDT, which is concurrent with previous research.33,34 The relationship between healthcare workers (HCWs) and patients is a vital component of medication adherence, meaning if done improperly, the risk of non-adherence increases.35–37 This is a particular issue when leprosy services are provided by HCWs with little experience in the disease.38–40 It is therefore vital that programmes and interventions to reduce leprosy transmission involve assessing the baseline knowledge of HCWs involved, and providing sufficient, culturally sensitive training where necessary. Pilot studies have also shown greater access to HCWs via telephone helplines resulted in improved adherence, as patients were able to address issues including ADRs when they arose.41,42 This shows the potential for tele-health programmes to improve patient education and support with subsequent improvement in adherent behaviour.

Other forms of counselling should also be explored for improving adherence. Peer counselling (people counselled by others with shared experience) for people diagnosed with leprosy has been utilised in Indonesia to reduce leprosy-related stigma on both personal and community levels.43 Studies have shown that peer counsellors for conditions such as diabetes and HIV resulted in improved medication adherence and service retention rates.44 To date, no such studies have been published for leprosy. Considering the beneficial effects peer counsellors have on improving stigma-related outcomes, their effects on medication-outcomes should be explored further.

Another key theme that transcended the identified factors was stigma, which manifested in various ways. One way was how stigma affected access to services, with patients with leprosy travelling to distant services for treatment. It can be anticipated that stigma reduction and a
more positive attitude towards leprosy will not only encourage patients to attend services in general, but to also attend local services. This will remove other barriers to accessing MDT such as transport costs.

Leprosy-associated stigma is complex, with high variation on how this presents, both between countries and within countries.\textsuperscript{38,45} One common feature is how the lack of knowledge and understanding of the disease (e.g. cause and transmission) can exacerbate stigma.\textsuperscript{38,39,46,47} Behavioural change and education interventions have been successful in reducing leprosy-associated stigma.\textsuperscript{48} Many have focussed on encouraging health-seeking behaviour.\textsuperscript{49} However, others found how improved understanding of leprosy and enhanced community support though regular education can positively influence adherence to MDT.\textsuperscript{50}

Another way stigma manifested is through hyperpigmentation secondary to clofazimine use in MB leprosy. The reasons for this effect causing non-adherence are dependent on location. For example, studies based in Brazil found differing reasons for hyperpigmentation resulting in patients showing non-adherence, including increased difficulty for laborers to work in hot conditions and racial abuse.\textsuperscript{51,52} Current WHO guidelines for the treatment of leprosy recommends the addition of clofazimine to MDT for PB leprosy, which has divided opinion.\textsuperscript{3,53,54} Any benefits of adding clofazimine must be offset against the increased risk of non-adherence, and stigma secondary to hyperpigmentation should not be underestimated. The decision to add clofazimine should be made on a country-level basis, allowing individual countries to assess the benefits of adding clofazimine against any culturally dependent risk of non-adherence.

This review found that the proportion of women included in studies was lower than men. This reflects wider issues of women having inequitable access to leprosy services.\textsuperscript{55,56} The use of active case finding seen in one study led to a more equal gender split in participants, which is in line with other research.\textsuperscript{57,58} However, the diagnosis of leprosy is only the beginning of the journey to recovery. Although active case finding is effective in identifying new cases in women, traditional barriers to healthcare access still prevent women continuing MDT long-term. The current WHO global action plan for leprosy recognizes this and advises that women should be supported financially to access health services.\textsuperscript{59} Although this will be helpful in some cases, it does not appreciate other barriers to women accessing services. Therefore, other approaches to improve access to MDT need to be considered, such as outreach and delivery services, which have been shown to be effective both in leprosy and in other health issues.\textsuperscript{20,60}

There were a couple of limitations identified for this review. Firstly, the heterogeneity between the quantitative studies meant that a meta-analysis was not possible. Therefore, a non-quantitative review was performed, which is more prone to bias.

Secondly, the studies included only represented 3 WHO SEARO member states and other states with considerable disease burden were not represented. Due to the sociocultural nuances of leprosy, it is difficult to extrapolate the findings of this review to all individual WHO SEARO member states.

In conclusion, there are diverse and complex factors that result in non-adherence to MDT, and no single intervention will address these. It is clear that wider structural issues need to be addressed to improve adherence. These include: ensuring continued access to MDT (particularly for patients at high-risk of non-adherence), ensuring patients are adequately informed about leprosy and MDT, and minimizing the stigma of leprosy.

**Ethical approval**

Not required for systematic reviews.
Disclosure of conflict of interest
The authors report no conflicts of interest.

Funding
No funding was paid for this research.

Authorship and contribution
TM performed the literature search, analysed the data and wrote the body of text. As guarantor, he accepts full responsibility for the work and the conduct of the study, had access to the data and controlled the decision to publish.

GD as supervisor provided guidance in the study design, search strategies, quality analysis of studies. In addition, she edited the paper and assisted in analyzing the study findings.

Patient consent
No patient consent was required.

Review registry
The review was registered with PROSPERO. The registration number for the review is CRD42021242092 and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=242092. The review adhered to the PRISMA guidelines for systematic reviews.

Acknowledgements
The authors would like to thank the librarians at the Brighton and Sussex Medical School for assisting in obtaining articles for the review.

References


Appendix A. Search strategies used in the literature review

EMBASE

(((exp LEPROSY/OR “MYCOBACTERIUM LEPRAE”/OR (“hansen disease” OR “hansen’s disease” OR “hansens disease”).af) AND (“MEDICATION COMPLIANCE”/OR “PATIENT COMPLIANCE”/OR (complian* OR adheren* OR concordan*).af)) AND (((DAPSONE/AND “CLOFAZIMINE DERIVATIVE”/) AND RIFAMPICIN/) OR (MDT OR “multi drug therapy” OR “multidrug therapy” OR “multi-drug therapy”).af)) [DT 1982-2021]

MEDLINE

(((exp LEPROSY/OR “MYCOBACTERIUM LEPRAE”/OR (“hansens disease” OR “hansen’s disease”).af) AND (“MEDICATION ADHERENCE”/OR (adheren* OR complian* OR concordan*).af)) AND (((CLOFAZIMINE/AND DAPSONE/) AND RIFAMPIN/) OR (MDT OR “multi-drug therapy” OR “multidrug therapy” OR “multi drug therapy”).af)) [DT 1982-2021]

PUBMED

((leprosy[MeSH Terms]) OR (leprosy)) AND ((compliance, medication[MeSH Terms]) OR (complian*) OR (adheren*) OR (concordan*)) AND ((MDT) OR (“multi drug therapy”) OR (“multi-drug therapy”)) AND (“1982/01/01”[Date - Publication]: “2021/07/01”[Date - Publication])

PSYCHINFO

(((leprosy OR “hansen disease” OR “hansens disease” OR “hansen’s disease” OR “mycobacterium leprae”).af) AND (“TREATMENT COMPLIANCE”/OR COMPLIANCE/OR “TREATMENT DROPOUTS”/OR “TREATMENT REFUSAL”/OR (complian* OR adheren* OR concordan*).af)) AND (MDT OR “multi drug therapy” OR “multidrug therapy” OR “multi-drug therapy”).af) [DT 1982-2021]

GLOBAL HEALTH


Appendix B. Summary of quality appraisals
<table>
<thead>
<tr>
<th>Rating question</th>
<th>Mushtaq</th>
<th>Kumar¹⁵⁰</th>
<th>Hajid</th>
<th>Susanti</th>
<th>Heynders</th>
<th>Raju</th>
<th>Kumar¹⁵²</th>
<th>Saraswat</th>
<th>Rao</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Is the source population or source area well described?</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>1.2 Is the eligible population or area representative of the source population or area?</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1.3 Do the selected participants or areas represent the eligible population or area?</td>
<td>NA</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>NA</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>2.1 Selection of exposure (and comparison) group. How was selection bias minimised?</td>
<td>NR</td>
<td>+</td>
<td>NR</td>
<td>−</td>
<td>+</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>−</td>
</tr>
<tr>
<td>2.2 Was the selection of explanatory variables based on a sound theoretical basis?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2.3 Was the contamination acceptably low?</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2.4 How well were likely confounding factors identified and controlled?</td>
<td>NR</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2.5 Is the setting applicable to the UK?</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3.1 Were the outcome measures and procedures reliable?</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>3.2 Were the outcome measurements complete?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3.3 Were all the important outcomes assessed?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>3.4 Was there a similar follow-up time in exposure and comparison groups?</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3.5 Was follow-up time meaningful?</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4.1 Was the study sufficiently powered to detect an intervention effect (if one exists)?</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>NR</td>
<td>−</td>
</tr>
<tr>
<td>4.2 Were multiple explanatory variables considered in the analyses?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>4.3 Were the analytical methods appropriate?</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>NR</td>
<td>−</td>
</tr>
<tr>
<td>4.4 Was the precision of association given or calculable? Is association meaningful?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>5.1 Are the study results internally valid (i.e., unbiased)?</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>5.2 Are the findings generalisable to the source population (i.e. externally valid)?</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>
Table B.2. Summary of quality appraisals for qualitative studies

<table>
<thead>
<tr>
<th>Rating question</th>
<th>Heijnders¹⁴¹</th>
<th>Heijnders¹⁴²</th>
<th>Susanto</th>
<th>Lal</th>
<th>Correia</th>
<th>Chalise</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is a qualitative approach appropriate?</td>
<td>Appropriate</td>
<td>Appropriate</td>
<td>Appropriate</td>
<td>Appropriate</td>
<td>Appropriate</td>
<td>Not sure</td>
</tr>
<tr>
<td>2. Is the study clear in what it seeks to do?</td>
<td>Clear</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Clear</td>
<td>Mixed</td>
</tr>
<tr>
<td>3. How defensible/rigorous is the research design/methodology?</td>
<td>Defensible</td>
<td>Defensible</td>
<td>Defensible</td>
<td>Defensible</td>
<td>Defensible</td>
<td>Not sure</td>
</tr>
<tr>
<td>4. How well was the data collection carried out?</td>
<td>Inadequately reported</td>
<td>Appropriately</td>
<td>Appropriately</td>
<td>Inadequately reported</td>
<td>Appropriately</td>
<td>Inadequately reported</td>
</tr>
<tr>
<td>5. Is the role of the researcher clearly described?</td>
<td>Not described</td>
<td>Not described</td>
<td>Clearly described</td>
<td>Not described</td>
<td>Not described</td>
<td>Not described</td>
</tr>
<tr>
<td>6. Is the context clearly described?</td>
<td>Not sure</td>
<td>Not sure</td>
<td>Not sure</td>
<td>Unclear</td>
<td>Not sure</td>
<td>Not sure</td>
</tr>
<tr>
<td>7. Were the methods reliable?</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
</tr>
<tr>
<td>8. Is the data analysis sufficiently rigorous?</td>
<td>Rigorous</td>
<td>Rigorous</td>
<td>Rigorous</td>
<td>Not reported</td>
<td>Rigorous</td>
<td>Not reported</td>
</tr>
<tr>
<td>9. Is the data &quot;rich&quot;?</td>
<td>Rich</td>
<td>Rich</td>
<td>Rich</td>
<td>Poor</td>
<td>Rich</td>
<td>Poor</td>
</tr>
<tr>
<td>10. Is the analysis reliable?</td>
<td>Not sure</td>
<td>Reliable</td>
<td>Not reported</td>
<td>Not convincing</td>
<td>Convinving</td>
<td>Not convincing</td>
</tr>
<tr>
<td>11. Are the findings convincing?</td>
<td>Convincing</td>
<td>Convincing</td>
<td>Convincing</td>
<td>Partially relevant</td>
<td>Relevant</td>
<td>Partially relevant</td>
</tr>
<tr>
<td>12. Are the findings relevant to the aims of the study?</td>
<td>Relevant</td>
<td>Relevant</td>
<td>Relevant</td>
<td>Partially relevant</td>
<td>Relevant</td>
<td>Partially relevant</td>
</tr>
<tr>
<td>13. Conclusions</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Not sure</td>
<td>Adequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>14. How clear and coherent is the reporting of ethics?</td>
<td>Appropriate</td>
<td>Appropriate</td>
<td>Appropriate</td>
<td>Inappropriate</td>
<td>Appropriate</td>
<td>Not reported</td>
</tr>
<tr>
<td>As far as can be ascertained from the paper, how well was the study conducted?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>
### Table B.3. Summary of quality appraisals for mixed methods studies

<table>
<thead>
<tr>
<th>Question</th>
<th>Kar\textsuperscript{93}</th>
<th>Raju\textsuperscript{153}</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1. Are there clear research questions?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>S2. Do the collected data allow to address the research question?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>1.1. Is the qualitative approach appropriate to answer the research question?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>1.2. Are the qualitative data collection methods adequate to address the research question?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>1.3. Are the findings adequately derived from the data?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>1.4. Is the interpretation of results sufficiently substantiated by data?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4.1. Is the sampling strategy relevant to address the research question?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4.2. Is sampling representative of the target population?</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
</tr>
<tr>
<td>4.3. Are the measurements appropriate?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4.4. Is the risk of non-response bias low?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4.5. Is the statistical analysis appropriate to answer the research question?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5.1. Is there an adequate rationale for using a mixed methods design to address the research question?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5.2. Are the different components of the study effectively integrated to answer the research question?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?</td>
<td>Can’t tell</td>
<td>Yes</td>
</tr>
<tr>
<td>5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>