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A systematic review of non-pharmacological interventions to improve therapeutic adherence in tuberculosis

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ABSTRACT

Background: Reviews examining non-pharmacological interventions to improve therapeutic adherence in tuberculosis have several limitations (design, quality assessment...). Consequently, for clinical practice, it is important to generate a review containing all the information to improve patient adherence, solving the previous issues.
Objectives: To examine non-pharmacological interventions to improve therapeutic adherence in tuberculosis through clinical trials.
Methods: A systematic review in MEDLINE/EMBASE was performed.
Results: Thirty seven papers were analysed. The disease treatment interventions were disparate, grouped into: education, psychological interventions, new technologies, directly observed treatment, incentives and improved access to health services. In the treatment of latent infection, the majority of studies were conducted in the marginal population (drug addicts, homeless individuals and prisoners) and were based mainly on the provision of incentives. Study quality was generally low.
Conclusions: Great variability exists in the studies comparing strategies for identifying interventions, objectives and effects. The designs carried out generally have methodological deficits.

Introduction[1]

Tuberculosis is produced by the bacillus *Mycobacterium tuberculosis*, also known as Koch's bacillus. Infection spreads through the air and the risk factors for infection are mainly contact with people who are ill, have autoimmune diseases, unhealthy lifestyles and social factors such as poverty, overcrowding and lack of hygiene.[1] This disease is the main cause of death from a curable infectious disease. When a person comes into contact with the bacillus, a primary infection occurs, which in most cases is asymptomatic. This latent infection can persist for many years until the onset of a trigger for disease reactivation.[2] One third of the world's population is believed to have a latent tuberculosis infection, and the lifetime risk of developing the disease is 5–10%. Treating latent tuberculosis infection is a key objective for tuberculosis control.[3]

In cases of latent tuberculous infection, treatment with isoniazid is given for a period of six to twelve months, varying from country to country, depending primarily on age and human immunodeficiency virus co-infection. Treatment of tuberculosis is generally based on the combination of four drugs: isoniazid, rifampicin, pyrazinamide, which are the essential drugs, accompanied by ethambutol. Treatment is divided into two parts: an intensive phase lasting two months, which includes all four drugs, and a maintenance phase with isoniazid and rifampicin until the end of the treatment, which lasts between six and twelve months.[4,5]

One of the main problems in controlling the disease is nonadherence to treatment. Lack of adherence is also contributing to the emergence of multidrug-resistant tuberculosis, i.e., resistant to rifampicin and isoniazid. In 2016, 83% of patients who started treatment for tuberculosis successfully completed it.[3] To attempt to prevent the spread of this epidemic, multiple strategies have been put in place, one of the most important of which is the DOT (Directly Observed Therapy) strategy implemented by the World Health Organization in 1991,[3] used mainly in developing countries.

In conjunction with this type of strategy, multiple studies have been designed and carried out to improve adherence to treatment, which have been studied through systematic reviews.[6–16] The strategies used have been very varied, but they can be grouped into techniques to modify behaviour through behavioural reinforcement using education or incentives (money, food, vouchers for transport), and techniques to improve the organisational system (bringing the points of care closer to the population living far from the treatment clinics,

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[1] DOT (Directly Observed Therapy), RCT (controlled clinical trials)

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the possibility of choosing where medication is administered in DOT cases).

Reviews that have examined non-pharmacological interventions to improve tuberculosis treatment adherence vary greatly in their design,[6-16] as they have considered studies with non-randomised or observational designs, have focused only on latent infection or treatment, have addressed only one type of intervention (e.g. new technologies), have not all examined the quality of the included studies, and have conducted meta-analyses of different interventions in non-homogeneous populations. We carried out a systematic review of the scientific literature evaluating only studies that assessed the intervention using the most powerful design (controlled clinical trials, RCTs), that assessed any type of non-pharmacological intervention, distinguishing between latent tuberculosis infection and active tuberculosis, and determining the quality of the studies. Accordingly, we have generated a document that collects all the available information on the type of interventions available to improve patient therapeutic adherence and thus reduce bacterial resistance and the spread of the disease. This is important in clinical practice because health care professionals will be able to determine the best option to achieve compliance with the prescribed treatment according to the individual patient characteristics. This should then lead to cure of the tuberculosis, with a reduction in latent infections and bacterial resistance.

Methods

This systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[17]

Search strategy

We conducted a systematic review to identify studies that compared non-pharmacological interventions (clinical trials) used to increase adherence of treatment for people with active tuberculosis and latent tuberculosis infection. The MEDLINE database (through Pubmed) and EMBASE were analysed using the following keywords linked by connectors (Supplemental Material): tuberculosis, compliance, adherence, anti-bacterial agents and antibiotic.

Articles were restricted to those published in English or Spanish that had abstracts and that had also been indexed as clinical trials in MEDLINE and EMBASE (clinical trials in filters). The search was conducted including all articles published before 31 December 2018. In addition, references of all papers potentially relevant to meeting our primary objective were analysed. We also examined systematic reviews that assessed methods to improve therapeutic adherence in tuberculosis,[6-16] in order to complete our search and thus have the maximum scientific evidence available, since it is possible that using our keywords some papers were not identified that had been considered in previous systematic reviews. Reviews done by others are not themselves included, although the articles included in these previous reviews were also checked by us to determine whether they adjusted to our inclusion or exclusion criteria, as was done by others for their reviews.[6-16]

Inclusion and exclusion criteria

We selected those scientific papers that used a randomised experimental design to analyse the efficacy of interventions to improve therapeutic adherence in tuberculosis, both in active tuberculosis and latent infection. The following exclusion criteria were established: pilot studies, non-experimental designs (observational or quasi-experimental), descriptive studies of the trial assessing factors associated with adherence, and study protocols.

Study selection

Two researchers independently and in parallel examined titles and abstracts to exclude articles that did not meet the inclusion criteria established in the study. After reaching a consensus on all the potential scientific studies to achieve our main objective, the articles were examined in full text.

Analysis of the full-text papers was also conducted independently and in parallel by the same two researchers, who determined whether the paper met all the inclusion criteria and none of the exclusion criteria. The results obtained were agreed upon by the two reviewers, and if discrepancies were found, these were analysed by a third researcher. This analysis was followed by the extraction of results of interest from the selected publications.

Data extraction

For each paper selected, we first determined whether it referred to patients with latent infection, active tuberculosis or both, stratifying the results by this component. The following characteristics were then extracted: country, treatment duration, intervention(s) performed, definition of the control group, sample size in each group, outcome, proportion of therapeutic adherence in the groups, and effect of the intervention on adherence (beneficial, neutral or harmful).

As outcomes, the following parameters were considered, which were entirely related to therapeutic adherence: treatment completed, treatment success, percentage of taken/missed doses, pill count, isoniazid in urine, sputum smear conversion and medication taken on time. Treatment success was defined as the sum of patients clinically cured of the infection (positive sputum culture at the beginning of the treatment that is negative in the last month of treatment or on at least one previous occasion) or who have completed the treatment (with no results from the sputum culture either in the last month or on a previous occasion).[18] In the event that the work assessed success and completion of treatment separately, only success was studied in our review, as this provided more information on taking the medication.

Quality assessment (risk of bias)

The Cochrane Collaboration's tool for assessing risk of bias in randomised trials was used to assess the quality of the clinical trials included in our review. This tool evaluates seven aspects of RCT design with regard to the risk of possible biases: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and researchers (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. These aspects are assessed with three possibilities (high, low and unclear) that measure the risk of this type of bias. Once all risks are assessed, an overall quality assessment is generated using the “worst score counts” principle. This means that the poorest score of all items should be given as an overall score.[19] For example, if a study obtains a high risk in any of the aspects, it is classified as high risk overall.

In particular for our systematic review, we emphasize that performance bias is meaningless in the type of interventions analysed,[6-16] as these are mainly educational measures, new technologies, DOT, provision of incentives and healthcare management, because clearly we cannot mask the intervention to the patients or researchers. For example, a patient will know perfectly well whether he or she has received any financial or non-financial incentives.

The Cochrane Collaboration's tool for assessing risk of bias in randomised trials includes a section on other biases, which is left to the discretion of the evaluator on other aspects not covered in the other six aspects above. In this section we mainly considered whether the researchers had calculated the number of patients needed (sample

size) to determine with sufficient power whether the intervention was effective in improving therapeutic adherence. In the event this size was not calculated, a high risk of bias was considered to exist, since for any clinical study it is necessary to obtain results with a low type I and II error.[20] Furthermore, if the size had been calculated and the necessary number of patients was not achieved in recruitment, this was considered a high risk of bias.

Data synthesis

The data were analysed using a descriptive analysis of the variables extracted from each publication, distinguishing between treatment of latent infection or of active tuberculosis. A meta-analysis was not performed as there was a wide variability in designs, interventions and patients. This heterogeneity was previously indicated in another systematic review,[6] and the authors, just as we did, analysed the risk of bias and at a descriptive level all the extracted characteristics.

Results

We began with 433 scientific papers from the MEDLINE and EMBASE databases (Fig. 1), together with an additional 29 papers from the systematic reviews consulted and which were not on the list of titles and abstracts of the two databases analysed. From the sum of these (462) the duplicates were eliminated, leaving a total of 375 articles for screening in title and abstract. After this screening, we excluded 306 in which neither the title nor the abstract indicated that they had developed an intervention of the proposed characteristics, which left a total of 69 articles that were analysed in full text.[21-89] Following this analysis, 32 papers were excluded.[21-52] Of the 32 excluded studies three were conducted only in children,[21-23] three were RCT protocols,[24-26] two were RCTs assessing pharmacological interventions,[27,28] four were quasi-experimental studies,[29-32] one was a pre-experimental study,[33] one was a single semi-randomized study,[34] one had a before and after design,[35] one was non-randomized,[36] in another, no intervention was performed,[37] in one study, the intervention was not carried out in all participants,[38] another was a qualitative evaluation,[39] in two studies, attendance at the visit was evaluated,[40,41] in two studies adherence was evaluated according to medication not being collected,[42,43] in one study the definition of the outcome was different from the result obtained,[44] and finally we found eight purely descriptive studies.[45-52] After all these exclusions, a total of 37 papers were evaluated qualitatively.[53-89]

Analysis of the papers included in our review was stratified according to whether treatment was for active tuberculosis (Table 1) or latent tuberculosis infection (Table 2).[53-89] Concerning the treatment of active tuberculosis (Table 1) (28 papers),[53-58,60-65,67-69,71-75,77,78,83,84,86-89] it should be noted that all the interventions were carried out in the general population and mainly in countries with a high incidence of tuberculosis, which are developing countries. The studies analysed were published between 1990 and 2017. Treatment duration was generally between six and nine months with widely varying interventions. However, they can be grouped into several categories: education (training for non-health workers or volunteers on tuberculosis, educational programmes on patient adherence, training health professionals),[58,63,64,69,72,89] psychological support (self-help groups and self-esteem counselling),[54,74] new technologies (messages to the mobile phone of the patient and medication event monitoring systems),[53,55,56,78] DOT (by family members, volunteers, health workers

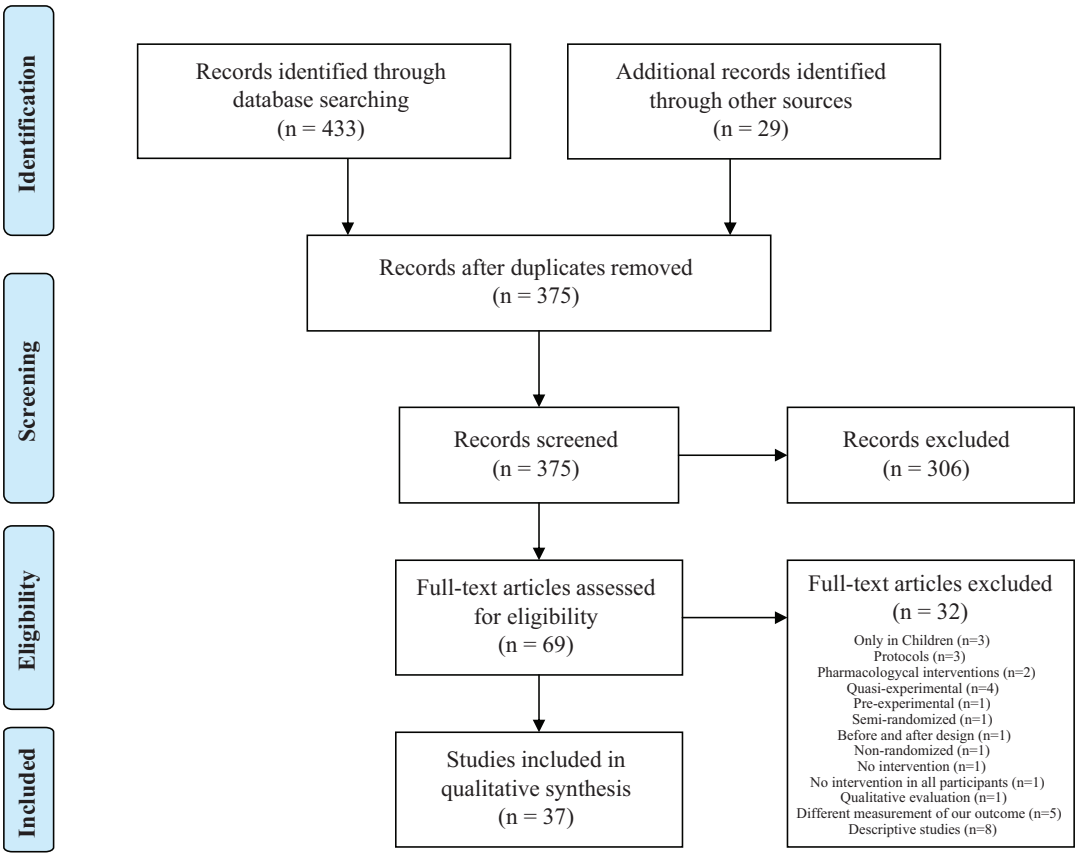

Fig. 1. Flow chart of the systematic review to determine non-pharmacological intervention studies to improve therapeutic adherence in tuberculosis.
Other sources: papers from the systematic reviews consulted and which were not on the list of titles and abstracts of the two databases analysed (MEDLINE and EMBASE). Of the final papers, 13 were obtained through the systematic reviews analysed.

Table 1
Articles included in our systematic review assessing therapeutic adherence for tuberculosis.

Reference	Country	Time, months	Intervention	Control	*n*, intervention	*n*, control	Outcome	Adherence (%), intervention	Adherence (%), control	Effect
Fang et al.[53]	China	6	SMS	Standard care (DOT)	160	190	Treatment completed	96.2	86.8	Beneficial
Tola et al.[54]	Ethiopia	6	Psychological counseling and education	Standard care (DOT)	368	330	Treatment completed (VAS scale)	90.5	74.6	Beneficial
Mohammed et al.[55]	Pakistan	6	SMS	Standard care	1110	1097	Treatment success	83	83	Neutral
Liu et al.[56]	China	6	SMS MEMS	Standard care	1008 SMS 997 MEMS 1064 Both	1104	<20% doses missed	72.7 83 86.1	71.1	Neutral
Ricks et al.[57]	USA	6–9	DOT by former substance users in recovery	DOT by health care workers	48	46	Treatment completed	85	61	Beneficial
Ritchie et al.[58]	Malawi	Not given	C1: A knowledge translation alone C2: A knowledge translation with a lay health worker	Standard care	68 30	80	Treatment success	65 70	58	Neutral
Kunawararak et al.[60]	Thailand	6 18†	Phone reminder	Standard care (DOT)	30 19†	30 19†	Treatment success	100 100†	96.7 73.7†	Beneficial
Jahnavi et al.[61]	India	Not given	Food supplements	Standard care	50	50	Treatment completed	98	82	Beneficial
Martins et al.[62]	Timor-Leste	8	Food incentives	Standard care (DOT)	136	129	Treatment completed	76	78	Neutral
Datiko et al.[63]	Ethiopia	8	Health extension workers education	Standard care (DOT)	230	88	Treatment success	89.3	83.1	Beneficial
Clark et al.[64]	Turkey	6	Pharmacist education	Standard care	56	58	INH (urine) Pills count	80.4 88.7	42.3 85.8	Beneficial Neutral
Thiam et al.[65]	Senegal	8	To improve access to care	Standard care	778	744	Treatment success	87.7	75.7	Beneficial
Newell et al.[67]	Nepal	8	DOT by relatives	Community DOT	358	549	Treatment success	89	85	Neutral
Clarke et al.[68]	South Africa	6	DOT by lay health workers	Standard care (DOT)	75	89	Treatment success	81	75	Beneficial
Lewin et al.[69]	South Africa	6 8*	Staff training	Standard care (DOT)	600	577	Treatment success	60	61	Neutral
MacIntyre et al.[71]	Australia	6	DOT by relatives	Self-supervised	87	86	INH (urine) Treatment completed	74.7 96.6	77.9 90.7	Neutral
Niazi et al.[72]	Iraq	6	Community participation	Standard care (DOT)	86	86	Sputum smear conversion	97.7	80.2	Beneficial
Mohan et al.[73]	Iraq	6	Home visiting	Standard care	240	240	Sputum smear conversion Treatment success	92.9 94.2	75 76.7	Beneficial
Alvarez Gordillo et al.[74]	Mexico	6	Self-help groups	Standard care	44	43	>75% doses	97.7	81.4	Beneficial
Lwilla et al.[75]	Tanzania	8	DOT by volunteers	Standard care (DOT)	221	301	Sputum smear conversion	76	69.4	Neutral
Tandon et al.[77]	India	6	DOT by volunteers	Self-supervised	226	153	Treatment completed	85	54	Beneficial
Moulding et al.[78]	Haiti	12	Monitors with/without feedback	Self-supervised	64 59	Not given	Treatment completed	92.2 83.1	Not given	Not given
Walley et al.[83]	Pakistan	8	DOT by nurses DOT by relatives	Self-supervised	170 165	162	Treatment success	66.4 62.4	64.8	Neutral
Zwarenstein et al.[84]	South Africa	6 8*	DOT by nurses DOT by volunteers	Self-supervised	58 54	44	Treatment success	57 74	59	Neutral
Kamolratanakul et al.[86]	Thailand	6	DOT	Self-supervised	414	422	Treatment completed	84	76	Beneficial
Zwarenstein et al.[87]	South Africa	6 8*	DOT by nurses	Self-supervised	78 33	82 23	Treatment success	59 42	56 74	Neutral Harmful
Paramasivan et al.[88]	India	6	Indirect defaulter retrieval method	Standard care	100	100	Treatment completed	88	73	Beneficial
Morisky et al.[89]	USA	6–9	Education and economic incentives	Standard care	43	45	Treatment completion	97.7	91.1	Neutral

Abbreviations: C, condition; DOT, Directly Observed Treatment; INH, isoniazid; MEMS, Medication Event Monitoring System; SMS, Short Message Service; USA, United States of America; VAS, Visual Analogue Scale.
All studies were carried out in the general population, except that by Ricks et al.[57], which was performed in substance users.
* Retreated patients.
† Multidrug-resistant tuberculosis.

Table 2
Articles included in our systematic review assessing therapeutic adherence for latent tuberculosis infection (all were carried out in the United States of America).

Reference	Population	Time, months	Intervention	Control	*n*, intervention	*n*, control	Outcome	Adherence (%), intervention	Adherence (%), control	Effect
Hirsch-Moverman et al.[59]	General	9	Peer-based intervention	Standard care	128	122	Treatment completion	60.9	56.6	Neutral
Nyamathi et al.[66]	Homeless	6	Nurse-case managed with incentives program	Standard care with incentives	279	241	Treatment completion	61.5	39.3	Beneficial
Tulsky et al.[70]	Homeless	6	Cash incentives	Non-cash incentives	65	54	Treatment completion	89.2	81.5	Neutral
Hovell et al., 2003[76]	Latino adolescents	6–9	Adherence coaching	Standard care	92	96	Treatment completion	51.1	37.5	Neutral
			Self-esteem counseling		98			41.8		
White et al.[79]	Inmates	6	Education	Standard care	107	104	Treatment completion	23 and 12	12	Beneficial for the incentives arm
			Non-cash incentives		114					
Chaisson et al.[80]	Injection drug users	6	DOT by nurses	Standard care	99	100	Treatment completion	80	79	Neutral
			Peer counseling		101			78		
Malotte et al.[81,*]	Drug users	6–12	C1: Outreach and incentive	C2: N/A	53	N/A	Treatment completion	52.8, 3.6 and 60	N/A	Beneficial (C1 and C3 vs C2)
							Medication taken on time	72, 12 and 69		
			Outreach only		55					
			C3: Incentive only		55					
Morisky et al.[82]	Adolescents	6	C1: Peer counseling	Standard care	199	195	Treatment completion	80.3	77.8	Neutral
			C2: Incentive contract		204			76.4		
			C3: C1+C2		196			84.8		
Tulsky et al.[85]	Homeless	6	Monetary incentives	Standard care	43	38	Treatment completion	44 and 19	26	Beneficial for the incentives arm
			Peer health adviser		37		Completion of 3 months of INH	71 and 42	45	
Morisky et al.[89]	General	9–12	Education and economic incentives	Standard care	58	59	Treatment completion	63.8	27.1	Beneficial

Abbreviations: DOT, Directly Observed Treatment; INH, isoniazid; N/A, not applicable.
* DOT was used in the three groups.

and teachers),[57,67,68,71,75,77,83,84,86,87] incentives (cash, food vouchers and transportation),[61,62,89] improvements in access to healthcare services (decentralise treatment centres and supervise health centres),[65] with the control group in most cases receiving the usual treatment according to the protocol of the country. Some of the papers presented more than one intervention or a combination of interventions compared with the control group.[56,58,78,83,84] Sample sizes in all groups varied greatly, ranging from 19 to 1110 patients. The outcome in most cases was treatment success, followed by treatment completion. Also assessed were the percentage of doses taken/missed, presence of isoniazid metabolites in urine, sputum conversion and tablet count. When evaluating the percentages of adherence between the intervention and control groups, we found 14 studies in which the intervention improved therapeutic adherence,[53,54,57,60,61,63,65,68,72-74,77,86,88] 11 that showed no effect (neutral),[55,56,58,62,67,69,71,75,83,84,89] another in which, depending on the outcome assessed, the effect changed from beneficial to neutral,[64] another study in which, depending on whether patients were treated for the first time or were re-treated, the effect could be neutral or harmful,[87] and finally there was one study in which we were unable to determine the effect, as the percentage of the control group was not reported in the paper.[78]

Table 2 analyses the characteristics of the studies found in the treatment of latent tuberculosis infection (1990–2013) (10 papers),[59,66,70,76,79-82,85,89] where most of the studies were carried out in the marginal population (drug addicts, homeless individuals and prisoners), with the exception of two studies carried out in the general population.[59,89] Much like for active tuberculosis, the duration of the intervention for latent infection was generally between six and nine months. However, for latent infection, the interventions were somewhat different from those for the treatment of active tuberculosis, as they were based mainly on the provision of incentives (mainly financial),[66,70,79,81,82,85,89] and the involvement of social services,[81] nursing and former patients who had already completed tuberculosis treatment and were acting as counsellors to the new patient.[59,80,82,85] The control group generally received standard care, and the sample size ranged from 37 to 279 patients. In this case the outcome used in all the studies was treatment completion and in two of these a second outcome was added.[81,85] Finally, with regard to the effect of the intervention, two studies were beneficial in improving adherence,[66,89] in three the benefit depended on the RCT arm (studies with more than one intervention),[79,81,85] and five studies were neutral.[59,70,76,80,82]

Table 3 shows the analysis of the quality of the studies analysed. We note that the fourth column is constant, since it is not possible to mask the intervention from the patient or the researcher, given its nature. The frequencies of low risk of bias in the different aspects were: random sequence generation, 22 (59.5%); allocation concealment, 14 (37.8%); blinding of outcome assessment, 35 (94.6%); incomplete outcome data, 24 (64.9%); and selective reporting, 36 (97.3%). The low risk of detection bias figure was very high as the evaluating team considered that the form of measurement was independent of knowledge of the intervention. Regarding other biases, the predominant error was not calculating the sample size or including fewer patients than required from the calculation performed. There were also other types of bias such as the presence of a civil war during the study (favouring a high rate of losses),[62] some patients not receiving the intervention correctly,[78] lack of a clear definition of the outcome,[72] changes in the protocol midway through the study,[85] and one study in which the authors doubted the accuracy of their results.[83] Overall there were six papers that had a low risk of bias (16.2%).[55,67,69,79,86,87]

Grouping the information collected in Tables 1-3 to only include studies with a low risk of bias,[55,67,69,79,86,87] we found that a single beneficial intervention could improve adherence,[86] and this is based

on DOT (where the patient could choose between health centre staff, a community member, or a family member) rather than self-supervising. However, while the intervention was beneficial in terms of improved adherence, it only changed adherence by 8%. Another study showed benefit in a single arm (non-financial incentives),[79] almost doubling adherence compared to the control group and the education arm, which had the same rate of adherence (23 vs. 12%). In the three that were neutral,[55,67,69] the interventions were technology,[55] DOT,[67] and education.[69] Finally, one study using DOT found a neutral effect on adherence for first-time treatment patients and a detrimental effect in those who were re-treated.[87]

Discussion

This study determined through a systematic review of only clinical trials (design with the most scientific evidence) the existing interventions in the literature that attempt to improve therapeutic adherence in tuberculosis, both in the treatment of active tuberculosis and latent infection. In addition, the quality of the work found was evaluated and was generally low. The results found, having not distinguished by type of intervention (DOT, technology or education), enable us to have the scientific evidence available in a single updated document. This document shows that few studies have been conducted rigorously and that the interventions designed by the authors have great variability (Tables 1-3).[53-89] All this indicates that there is room for improvement in clinical research.

We included only clinical trials in our review, rather than also including observational studies, which most of the other systematic reviews did.[6,7,9-12,14-16] Our research team decided to exclude these designs because they are not the most suitable way to assess an intervention and there is a greater risk of bias, since the results must be properly adjusted using multivariate models, and a large number of errors are made when these are applied in biomedical literature.[90] In fact, the type of review that gives us the most scientific evidence is the meta-analysis of clinical trials. We would like to point out that although we conducted a systematic review of clinical trials, we did not apply meta-analysis techniques. This is due to our having found enormous variability in the interventions designed by the different authors and applied to very different populations and health systems, as well as the high risk of bias in the studies themselves. Considering these factors, it is not entirely correct to apply mathematical techniques to the results obtained in the different studies. Even though we would have liked to do so, it is surprising that many studies do not include the absolute frequencies of the patients who complete the study or adhere to the therapy, although they do give the percentages. Two of the most recent systematic reviews have also not applied meta-analysis for the same reasons.[6,7]

Both active tuberculosis and latent infection treatment have been examined in this review, as we considered these two aspects to be important for the treatment of tuberculosis. However, we are aware that the interventions designed to treat active tuberculosis are in the general population for developing countries and for prophylaxis in the marginal population of the United States of America (Tables 1-2), although these are far fewer. Additionally, we eliminated from our study the clinical trials carried out in the paediatric population, since therapeutic adherence, for obvious reasons, is entirely influenced by parents.

When we compare the number of studies included in our review with that of the other systematic reviews,[6-16] we find that the number of clinical trials we included is much higher than that of these studies, ranging from 2 to 38, even though they assess a greater number of studies, as they also include studies with an observational design. This was expected, given that we included patients undergoing treatment both for active tuberculosis and for latent infection, and we did not distinguish between the types of intervention, although this meant analysing a greater number of scientific publications. Therefore, our work gathers all the information on what we can do to improve therapeutic adherence in tuberculosis.

Another important point is that we evaluated adherence preferentially through success in treatment, which includes cure plus completion of treatment.[18] However, studies that used success generally provided the number of patients who completed treatment. In our opinion, it is more important to evaluate success, since it is the most important clinical event for the patient. It is essential that both conditions are met, since the treatment can be taken and the patient not cured, which would not be satisfactory from a clinical point of view. Where studies were unable to assess success because the authors did not provide figures on which patients had been cured of the disease, we assessed medication taking. There are also other outcomes such as going to the appointment or picking up the medication from the at the consultation, which were not included in this review because we could not be sure that the patient had actually taken the prescribed treatment. Finally, we would like to point out that we included studies that assessed the isoniazid metabolite count,[64,71] sputum conversion,[72,73,75] tablet count and the percentage of doses taken/missed,[56,64,74] as they are entirely directly related to therapeutic adherence (Tables 1-2).

An important point to note is the fact that various studies have produced contradictory results, that is to say that the effect changed according to the type of study population[87] or the outcome analysed.[64] Concerning the type of population, the study by Zwarenstein et al.[87] found a neutral effect for patients treated for the first time and a prejudicial effect for patients who had already undergone treatment. The authors attributed this to the fact that the retreated patients had a bad prior experience with the treatment and that this demoralisation resulted in lack of treatment adherence.[87] On the other hand, the study by Clark et al.[64] found that the intervention was very beneficial in the patients who underwent urinary isoniazid (INH) measurements and neutral for medication counting. The authors make no mention of this in their manuscript,[64] but we consider that the differences could be due to the fact that the patients took their medication just before their control visit, where the usual analysis was done, and that for the pill count they provided an empty package to please the health care professional, which explains why the urinary INH measurements did show differences.

Our review only assesses treatment adherence, unlike other already published reviews that have assessed additional information, such as case finding, factors associated with adherence and impact on economic cost.[6-16] These results are also important for tuberculosis treatment, but should be studied in a different type of systematic review. Also, some of these reviews have focused on a single type of intervention, that is, they have eliminated mixed strategies, which do not enable distinguishing the reason why adherence improves/worsens. Working with all types of interventions, we obtain a more complete analysis of these cases, since there could be interaction between the different types of intervention and the combined effect could be much greater than if they were given separately.

We were very concerned that most of the studies have carried out the clinical trial without calculating the sample size or if they have done so, some have recruited a smaller number of patients than the number predetermined in this calculation (Table 3). This results in a significant increase in random error and therefore unreliable results,[6] as the results do not have the power to answer the question of whether the designed intervention improves therapeutic adherence. Consequently, there is a significant systematic error that has not been taken into account in a large number of the studies and, in fact, previous reviews did not assess this,[6-16] although one did mention it.[10] With regard to the rest of the possible biases in the included clinical trials, we would like to point out that there is very low quality in general, with only one study being found to be of good quality, where

Table 3
Risk of bias analysis of the papers included in the systematic review using the Cochrane Collaboration's tool.

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)*	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Overall
Fang et al.[53]	Unclear	Unclear	Not possible	Low	Low	Low	High (sample size calculation)	High
Tola et al.[54]	Unclear	Unclear	Not possible	Low	Low	Low	High (the sample size was less than the previous calculation with a power of 80%; the intervention started one month after the treatment)	High
Mohammed et al.[55]	Low	Low	Not possible	Low	Low	Low	None	Low
Liu et al.[56]	Low	Unclear	Not possible	Low	Low	Low	None	Unclear
Ricks et al.[57]	Low	Low	Not possible	Low	Low	Low	High (sample size calculation)	High
Ritchie et al.[58]	Low	Low	Not possible	Low	High	Low	High (the sample size was less than the previous calculation with a power of 80%; not all lay health workers completed the training and several of them were lost during the study)	High
Hirsch-Moverman et al.[59]	Unclear	Unclear	Not possible	High	Low	Low	High (sample size calculation)	High
Kunawararak et al.[60]	Unclear	Unclear	Not possible	Low	Low	Low	High (sample size calculation)	High
Jahnavi et al.[61]	Low	Unclear	Not possible	Low	Low	Low	High (sample size calculation)	High
Martins et al.[62]	Low	Low	Not possible	Low	Low	Low	High (civil conflict during the study with a lot of losses)	High
Datiko et al.[63]	Low	Unclear	Not possible	Low	Low	Low	None	Unclear
Clark et al.[64]	Unclear	Unclear	Not possible	Low	Unclear	Low	High (sample size calculation)	High
Thiam et al.[65]	Low	Unclear	Not possible	Low	High	Low	None	High
Nyamathi et al.[66]	High	High	Not possible	Low	Low	Low	None	High
Newell et al.[67]	Low	Low	Not possible	Low	Low	Low	None	Low
Clarke et al.[68]	Low	High	Not possible	Low	High	Low	None	High
Lewin et al.[69]	Low	Low	Not possible	Low	Low	Low	None	Low
Tulsky et al.[70]	Low	Low	Not possible	Low	Low	Low	High (power of the contrast 67% with the collected sample)	High
MacIntyre et al.[71]	High	High	Not possible	Low	High	Low	None	High
Niazi et al.[72]	High	High	Not possible	Low	Low	Low	High (heterogeneity in the groups; unclear definition of the outcome; sample size calculation)	High
Mohan et al.[73]	Unclear	Unclear	Not possible	Low	Low	Low	None	Unclear
Alvarez Gordillo et al.[74]	Low	Unclear	Not possible	Low	Low	Low	None	Unclear
Lwilla et al.[75]	Unclear	Unclear	Not possible	Low	High	Low	High (the sample size was less than the previous calculation with a power of 80%)	High
Hovell et al.[76]	Unclear	Unclear	Not possible	Low	Low	Low	High (power of the contrast 38% with the collected sample)	High
Tandon et al.[77]	Unclear	Unclear	Not possible	Low	High	Low	High (sample size calculation)	High
Moulding et al.[78]	Low	Unclear	Not possible	High	Unclear	High	High (sample size calculation; part of one group did not receive the intervention)	High
White et al.[79]	Low	Low	Not possible	Low	Low	Low	None	Low
Chaisson et al.[80]	Low	Unclear	Not possible	Low	Low	Low	High (sample size calculation)	High
Malotte et al.[81]	Low	Low	Not possible	Low	Low	Low	High (sample size calculation)	High
Morisky et al.[82]	Unclear	Unclear	Not possible	Low	Unclear	Low	High (sample size calculation)	High
Walley et al.[83]	Low	Low	Not possible	Low	High	Low	High (the authors are not sure about the precision of their results)	High
Zwarenstein et al.[84]	Low	Low	Not possible	Low	High	Low	High (the sample size was less than the previous calculation with a power of 80%)	High
Tulsky et al.[85]	Low	Low	Not possible	Low	Low	Low	High (sample size calculation; protocol change in the middle of the study)	High
Kamolratanakul et al., 1999[86]	Low	Low	Not possible	Low	Low	Low	None	Low
Zwarenstein et al.[87]	Low	Low	Not possible	Low	Low	Low	None	Low
Paramasivan et al.[88]	Unclear	Unclear	Not possible	Low	Unclear	Low	High (sample size calculation)	High
Morisky et al.[89]	High	High	Not possible	Low	Unclear	Low	High (sample size calculation)	High

* Given the nature of the intervention, blinding was not possible.

the intervention had been beneficial.[86] All this shows us that new studies are needed that correctly design interventions to improve therapeutic adherence and thus reduce the possible bacterial resistance and the spread of the disease.

The clinical implication of the results of this review relates to the choice of the health care professional of the type of intervention in order to achieve a positive effect on treatment adherence. Firstly, the target population should be compared with that of the studies included in this review, as if they are very disparate there will be no evidence to be able to apply the intervention. For example, we cannot apply an intervention that has been effective in homeless persons to the general population, or populations with a high prevalence of infectious diseases, such as in India, China or Thailand, compared with countries without such high prevalence rates, like USA or European countries. Secondly, we should check in the studies undertaken in populations similar to ours whether the study design was adequate, as if not, their results will not be so reliable for application in clinical practice. Another important point to determine, once the previous two have been corroborated, is whether we have the means available to apply the intervention in the same way it was applied in the original study. Finally, we will analyse the effect of the intervention on adherence, retaining only the interventions that had a beneficial effect on adherence. If no study fulfils these conditions, we shall have no evidence to select an intervention for our patients. This, then, would be a topic to be examined in future studies, for application in usual clinical practice.

Limitations of the study

Although we have been very rigorous in the analysis of the articles consulted, it is possible that we have not included all the articles, since we have used only EMBASE and MEDLINE, we have limited ourselves only to studies that are already published and we have been able to analyse only texts written in English or Spanish. This last point is important because, given that the disease is most prevalent in developing countries, it is possible that some authors in these countries may have written some form of publication in their native language. Finally, we indicate as a limitation not having applied the GRADE scale. This would help us to measure the quality of the evidence with knowledge of all the publications regarding one type of intervention.[91] However, given the wide variability and high risk of bias, the GRADE scale has not been used in this study.

Of the 37 scientific articles included in the final analysis we were surprised to have collected 13 of these from the other systematic reviews.[53,60,61,63,67,68,69,75,82-84,86,88] This could lead one to think that our bibliographic search had limitations. First, we have noted that our keywords (adherence and compliance) were not used by many of the authors. We chose these terms for our search as they are the scientific terms used (descriptors in both MEDLINE and EMBASE) to determine whether a patient takes the treatment following the guidelines. Second, this same situation is reflected in the rest of the systematic reviews analysed,[6-16] in which the authors obtained numerous studies following this same method. In addition, if we compile all the reviews and analyse the total number of RCTs finally included by excluding those papers that present any of our exclusion criteria,[6-16] none has as many RCTs as ours.

Conclusions

The studies found are in reality very different from each other. There is too much variability in studies on therapeutic adherence, both in the active tuberculosis and in the latent infection treatment groups, to be able to compare strategies for identifying interventions, objectives and effects. In addition, the designs generally have methodological flaws, preventing us from accurately determining which interventions we could apply in clinical practice for our patients. Accordingly, we encourage other authors to continue researching in this line, by developing new clinical trials, following the current recommendations that minimise the risk of bias, and all of this with a sample size that is adequate for its objective.[20] Once several studies of this nature have been carried out, we will be in a position to reassess the clinical question posed in this systematic review.

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Declaration of Interest statement

None.

Supplementary materials

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