

ORIGINAL ARTICLE

Methods to improve medication adherence in patients with chronic inflammatory rheumatic diseases: a systematic literature review

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ABSTRACT

Objective Lack of adherence to treatment is frequent in chronic inflammatory rheumatic diseases and is associated with poorer outcomes. The objective of this study was to describe and evaluate interventions that have been proposed to enhance medication adherence in these conditions.

Methods A systematic literature review was performed in Pubmed, Cochrane, Embase and clinicaltrials.gov databases completed by the rheumatology meeting (ACR, EULAR and SFR) abstracts from last 2 years. All studies in English or French evaluating an intervention to improve medication adherence in chronic inflammatory rheumatic diseases (rheumatoid arthritis (RA), spondyloarthritis (SpA), crystal related diseases, connective tissue diseases, vasculitis and Still's disease) were included. Interventions on adherence were collected and classified in five modalities (educational, behavioural, cognitive behavioural, multicomponent interventions or others).

Results 1325 abstracts were identified and 22 studies were finally included (18 studies in RA (72%), 4 studies in systemic lupus erythematosus (16%), 2 studies in SpA (8%) and 1 study in gout (4%)). On 13 randomised controlled trials (RCT) (1535 patients), only 5 were positive (774 patients). Educational interventions were the most represented and had the highest level of evidence: 8/13 RCT (62%, 1017 patients) and 4/8 were positive (50%). In these studies, each patient was individually informed or educated by different actors (physicians, pharmacists, nurses and so on). Supports and contents of these educational interventions were heterogenous.

Conclusion Despite the importance of medication adherence in chronic inflammatory rheumatic disorders, evidence on interventions to improve medication adherence is scarce.

INTRODUCTION

Adherence to long-term therapy can be defined by the extent to which a person's behaviour—taking medication, following a diet and/or executing lifestyle changes—corresponds with agreed recommendations from

Key messages**What is already known about this subject?**

- Medication non-adherence in chronic inflammatory rheumatic diseases is associated with poorer outcomes and important costs.

What does this study add?

- This systematic literature review reports that educational interventions do improve medication adherence in these conditions and have the highest level of evidence.

How might this impact on clinical practice?

- Educational interventions can be proposed to patients suffering of chronic inflammatory rheumatic diseases in order to optimise their medication adherence.
- Other types of interventions might be added but they need further good quality evaluation.

a healthcare provider.¹ It is a dynamic process in which the patient is involved to actively participate. It can be explained as a combination of the term 'compliance' which means 'taking the right dose at the right time' and the term 'persistence' which means 'taking the treatment continuously during the period of time prescribed'. However, we have to make the distinction between medication adherence and retention rate, which is a more complex notion often used as a surrogate effectiveness measure in observational studies (eg, registries). In the majority of studies, good adherence has been defined as taking 80% or more of the designated medication over the duration of the study time.²

Promoting adherence to treatment in chronic inflammatory rheumatic diseases is a critical yet challenging task for healthcare providers. First of all, lack of adherence is



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frequent in these diseases. For instance in RA, non-adherence can reach 20%–50% of all prescriptions.^{3–6} Furthermore, it has been shown that poor adherence is associated with poor outcomes in chronic diseases. In a recent article of the New York Times,⁷ lack of adherence was shown to be responsible for 125 000 deaths per year in the USA. In the same article, direct and indirect costs due to non-adherence were evaluated up to 100–289 billions of dollars in the USA. In RA, non-adherence is associated with a higher disease activity (DAS 28 and HAQ)⁸ which could lead to an increase of costs because of uncontrolled disease which may induce intensification of the treatment strategy. In view of the multiple negative implications of non-adherence, effective interventions to improve medication adherence are warranted.

Several modalities of interventions can be proposed in order to enhance medication adherence and can be classified in 4 categories: educational, behavioural, cognitive behavioural and multicomponent interventions.⁹ Educational interventions aim to enhance patient knowledge of the disease, the benefits and mechanisms of action of the medication regimen, the consequences of non-adherence and potential side effects of treatment. Behavioural interventions promote the act of medication taking and/or reinforce adherence by providing incentives for medication taking. Cognitive behavioural interventions intend to enhance adherence by modifying patients' thinking patterns that contribute to non-adherence while also establishing behavioural patterns that support adherence using aforementioned behavioural strategies. Based on motivational interviewing, these strategies explore the ambivalence between necessity beliefs and concern beliefs (fear of potential adverse events) in order to make the patient realise that taking the medication will improve his health. Finally, multicomponent interventions use multiple strategies to enhance adherence.

The objective of the present study was to describe the interventions that have been proposed to improve medication adherence in chronic inflammatory rheumatic diseases and to assess their efficacy.

METHODS

Systematic literature search and selection of the relevant studies

We performed a systematic review of the literature according to the Cochrane guidelines.¹⁰

Relevant publications were selected using PubMed, Embase and Cochrane databases without time limitation (up to February 2017). Associations of key words around the disease names and 'medication adherence' or 'patient compliance' were used (online supplementary table 1).

The search was completed by hand search using the references of the most relevant studies provided by the initiative's scientific committee of experts in the field. For unpublished data, a search to the American College of Rheumatology (ACR), European League against Rheumatism (EULAR) and French Society of Rheumatology

(SFR) meeting abstracts of the past 2 years was made (2016–2017) completed by a search on Clinicaltrials.gov.

To select the relevant studies first on abstracts then on full texts, we established the following inclusion criteria: adult, studies published in English or in French, diseases considered were: rheumatoid arthritis (RA), spondyloarthritis (SpA) including psoriatic arthritis (PsA), connective tissue diseases including systemic lupus erythematosus (SLE), crystal related diseases including gout and chondrocalcinosis, vasculitis including ANCA associated vasculitis, giant cell arteritis and polymyalgia rheumatica and Still's disease. Pharmacological medications considered were: conventional synthetic disease modifying antirheumatic drugs, biological DMARDs, immunosuppressive drugs (cyclophosphamide, among others), non-steroidal anti-inflammatory drugs, corticosteroids, colchicine and urate-lowering therapy. All design of studies assessing an intervention with the objective to enhance medication adherence were accepted. Reviews were not included. The flowchart shows this selection process (figure 1).

Data extraction

We collected data regarding the design of the studies: randomised or non-randomised, controlled or not, length of follow-up, number of patients in each group (intervention and control). Characteristics of the population were also collected: disease studied, disease duration, activity of the disease, age at baseline, gender, treatment studied. We then collected information on the intervention under evaluation: type of intervention aiming to improve medication adherence (educational, among others), main components and supports of this intervention, actors of the intervention, patients targeted by the intervention (systematic for all patients or targeted on patients considered to be non-adherent or at high risk of non-adherence). Tools used to measure adherence were noticed and finally, results on adherence were collected in each group of patient if available.

Analysis of the results

Effect sizes were not calculated due to the heterogeneity of the design of the majority of selected studies, that is, results were not pooled in a meta-analysis given the different adherence measures across studies. Results were then presented individually study by study.

RESULTS

Literature search and characteristics of included studies

According to the key words and after screening 1325 publications, 22 studies were finally included in the review (13 randomised controlled trials (RCT) (1535 patients) and 9 non-randomised studies (2397 patients)). The flowchart shows the selection process (figure 1).

We selected 18 studies in RA (72%), 4 studies in SLE (16%), 2 studies in SpA (8%) and 1 study in gout (4%). Educational interventions were the most represented in the selected studies: 11 studies (8 RCTs (1017 patients), 3 non-randomised studies (962 patients)). Only 2 studies

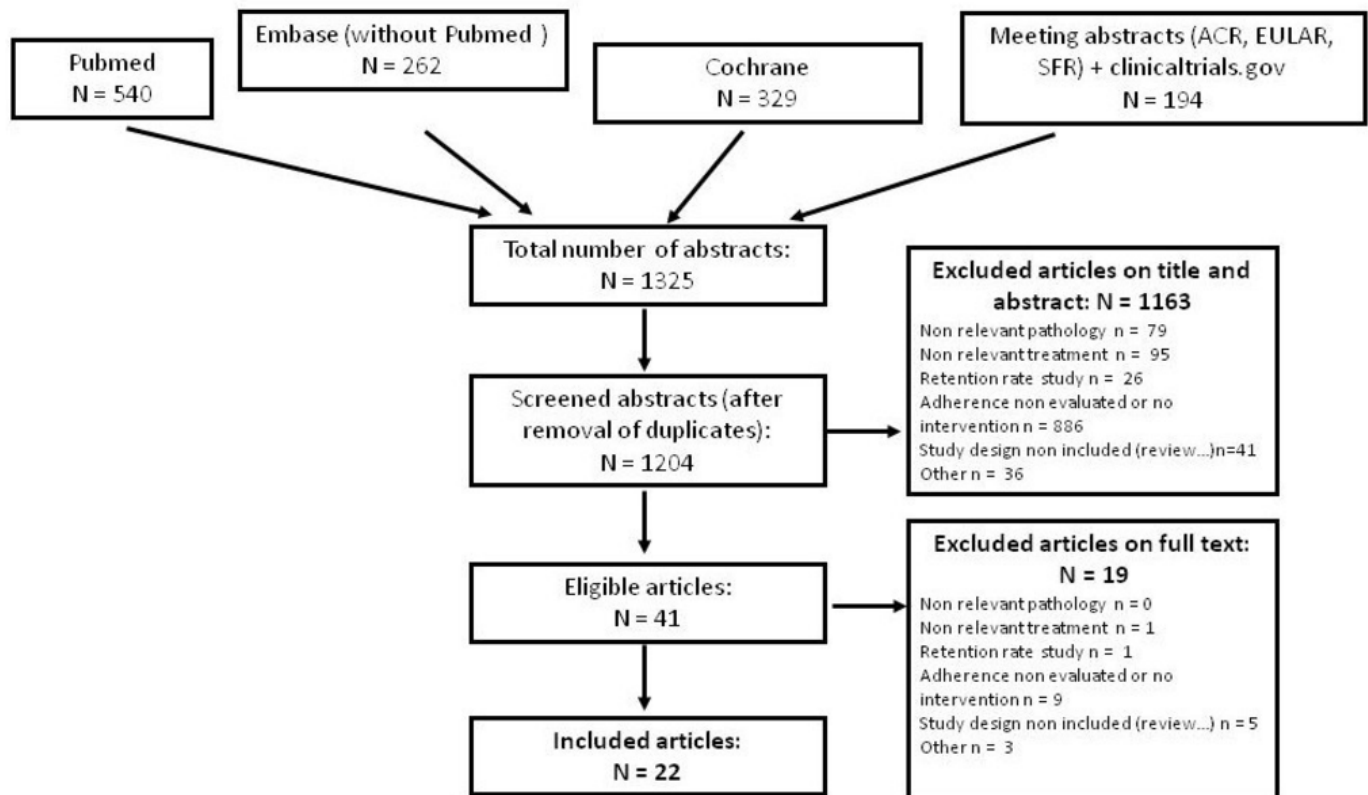


Figure 1 Flowchart of the selection process. ACR, American College of Rheumatology; EULAR, European League against Rheumatism; SFR, French Society of Rheumatology.

assessed a behavioural intervention (1 RCT (41 patients), 1 non-randomised study (201 patients)). Four studies assessed a cognitive behavioural intervention (3 RCTs (311 patients), 1 non-randomised study (69 patients)), only one study (686 patients) reported the effect of a multicomponent intervention and 4 studies (645 patients) reported other interventions which did not fulfil any type of the described interventions.

Educational interventions

Educational interventions were the most represented in the selected studies, and 6/11 studies were positive (table 1).

Among the eight selected RCTs, Hill *et al* reported that patients with RA who received a 6-month repeated education programme given by a nurse and based on oral and written information on the disease and the treatment were more adherent to D-penicillamine than control patients. In another RCT on RA,¹¹ patients who received an individual education using audio-visual supports (2 × 10 min) were more adherent to their treatment at 6 months (methotrexate, sulfasalazine, hydroxychloroquine (HCQ) ± corticosteroids) than patients from the control group. In a third RCT¹² focused on multiple chronic diseases including RA, a phone call given by a pharmacist 2 weeks after recruitment in order to provide information and counselling to the patient improved adherence to treatment at 4 weeks by comparison with usual care. Last positive RCT was performed in SLE.¹³

This study showed that targeted nursing by specialised nurses including an education during the hospitalisation, a personalised treatment plan and a follow-up after the hospital was better to improve adherence than regular specific nursing. However, these positive results were in balance with three RCTs which showed negative results: two of them assessed the efficacy of repeated collective education program in RA^{14 15} and the other proposed a multimedia support to educate RA patients.¹⁶

Homer *et al* compared individual education to collective education in a RCT,¹⁷ and found no difference between the two modes of educational intervention.

Among the non-randomised selected studies, in a longitudinal cohort study,¹⁸ Stockl *et al* showed that a RA disease therapy management program including repeated phone consultations by a pharmacist or by a nurse providing education associated with a mail service medication delivery, refill reminders by patient care coordinators and access to a pharmacist 24 hours a day, 7 days a week improved medication adherence to injectable RA medications by comparison with usual care. In a pilot study in gout,¹⁹ subjects completed a gout self-management knowledge examination at enrolment, 6 and 12 months. Each examination was followed by a nursing structured educational intervention and structured monthly follow-up calls from pharmacists emphasised adherence to management programs. Morisky's compliance scores improved from median baseline score at 6

Table 1 Summary of the studies included in the SLR

Author	Condition	Study design	Type of intervention/ Adherence assessment	Result
Hill <i>et al</i> , 2001 ³⁹	RA 91 patients	RCT, 6 months	<ul style="list-style-type: none"> ▶ Educational vs usual care ▶ Pharmacological marker 	At 6 months, 85% of the IG compared with 55% of the CG were taking their medication as prescribed (p<0.05)
Ravindran and Jadhav, 2013 ¹¹	RA 122 patients	RCT, 6 months	<ul style="list-style-type: none"> ▶ Educational vs usual care ▶ Morisky (MMAS-8) 	At 6 months, 98% of the IG were adherent compared with 83% in the CG (p=0.0003)
Clifford <i>et al</i> , 2006 ¹²	Multiple chronic diseases including RA 379 patients	RCT, 1 month	<ul style="list-style-type: none"> ▶ Educational vs usual care ▶ Patient report by phone 	At 1 month, 91% of the IG were adherent compared with 84% in the CG (p=0.032)
Zhang <i>et al</i> , 2016 ¹³	SLE 114 patients	RCT, 20 months	<ul style="list-style-type: none"> ▶ Educational vs usual care ▶ Likert scale (10 items, max=20 points) 	At 20 months, mean adherence score was 15.6 in the IG compared with 7.7 in the CG (p=0.033)
Brus <i>et al</i> , 1998 ¹⁴	RA 55 patients	RCT, 12 months	<ul style="list-style-type: none"> ▶ Educational vs usual care ▶ Pharmacy data 	No significant difference between IG and CG
Helliwell <i>et al</i> , 1999 ¹⁵	RA 77 patients	RCT, 12 months	<ul style="list-style-type: none"> ▶ Educational vs usual care ▶ Morisky (MMAS-4) 	No significant difference between IG and CG
Unk, 2014 ¹⁶	RA 108 patients	RCT, 1 month	<ul style="list-style-type: none"> ▶ Educational vs usual care ▶ MAQ 	No significant difference between IG and CG
Homer <i>et al</i> , 2009 ¹⁷	RA and PsA 62 patients	RCT	<ul style="list-style-type: none"> ▶ Individual education vs collective education ▶ Patient self-report and pill counts 	No significant difference between the two types of educational interventions
Stockl <i>et al</i> , 2010 ¹⁸	RA 732 patients	Longitudinal cohort study, 6 months	<ul style="list-style-type: none"> ▶ Educational vs usual care ▶ PDC 	At 6 months, mean PDC was 89% in the IG compared with 60% in the CG (p<0.001)
Fields <i>et al</i> , 2017 ¹⁹	Gout 45 patients	Single arm prospective non-controlled study, 12 months	<ul style="list-style-type: none"> ▶ Educational ▶ Morisky (MMAS-4) 	Morisky scores improved from median baseline score at 6 months and minimally further increased at 12 months
Van der Vaart <i>et al</i> , 2014 ²⁰	RA 105 patients	Non-randomised controlled study, 5 months	<ul style="list-style-type: none"> ▶ Educational vs usual care ▶ Morisky (MMAS) 	No significant difference between website users and non users
Ting <i>et al</i> , 2012 ²¹	SLE 41 patients	RCT, 14 months	<ul style="list-style-type: none"> ▶ Behavioural vs usual care ▶ Patient self-report, HCQ blood levels and pharmacy refill data 	No significant difference between IG and CG
Bruera <i>et al</i> , 2014 ²²	RA 201 patients	Prospective cohort study	<ul style="list-style-type: none"> ▶ Behavioural ▶ CQR 	Use of reminders was associated with better adherence especially in situations at high risk to forget the treatment
Evers <i>et al</i> , 2002 ²³	RA 59 patients	RCT, 12 months	<ul style="list-style-type: none"> ▶ Cognitive behavioural vs usual care ▶ Self report (3 points scale) 	At 12 months, significant increase in medication adherence in IG (p<0.05 baseline vs M12) Trend to decrease in medication adherence in CG (p=0.08)
Zwicker <i>et al</i> , 2014 ²⁴	RA 234 patients	RCT, 12 months	<ul style="list-style-type: none"> ▶ Cognitive behavioural vs usual care ▶ CQR, MARS and pharmacy refill data 	No significant difference between IG and CG

Continued

Table 1 Continued

Author	Condition	Study design	Type of intervention/ Adherence assessment	Result
Ferguson <i>et al</i> , 2015 ²⁵	RA 18 patients	RCT, 3 months	▶ Cognitive behavioural vs usual care ▶ MARS and Morisky	No significant difference between IG and CG
Feldman <i>et al</i> , 2016 ²⁶	RA and SLE 59 patients	Non-randomised, non-controlled study, 6 months	▶ Cognitive behavioural ▶ Morisky (MMAS-8)	At 6 months, there were no significant change in MMAS-8
Durcan <i>et al</i> , 2015 ²⁷	SLE 714 patients	Prospective non-controlled cohort study	▶ Multicomponent ▶ HCQ blood levels	Proportion of patients with HCQ blood levels > 500 ng/mL increased from 56% at baseline to 80% in patients who had 3 or more visits
Barton <i>et al</i> , 2016 ²⁸	RA 166 patients	RCT, 6 months	▶ Shared decision making vs usual care ▶ Self report (validated single-item measure)	No significant difference between IG and CG
Lofland <i>et al</i> , 2017 ²⁹	RA, PsA and chronic inflammatory bowel diseases 306 patients	Cohort study, 6 months	▶ Shared decision making vs usual care ▶ Morisky (MMAS-4)	At 6 months, mean MMAS-4 was 0.17 in IG vs 0.41 in CG (p=0.001)
Nota <i>et al</i> , 2016 ³⁰	RA and SpA 123 patients	Non-randomised study, 24 months	▶ Shared decision making vs usual care (historical comparison group) ▶ Morisky (MMAS-8)	No significant difference between IG and CG
Van den Bemt <i>et al</i> 2011 ⁴⁰	RA 50 patients	Prospective cohort study	▶ Making the rheumatologist aware of patients' non-adherence ▶ CQR	Making the rheumatologist aware of patients' non-adherence did not improve medication adherence

CG, control group; CQR, Compliance Questionnaire Rheumatology; HCQ, hydroxychloroquine; IG, intervention group; MARS, Medication Adherence Report Scale; MAQ, Medication Adherence Questionnaire; MMAS, Morisky Medication Adherence Scale; PDC, proportion of days covered; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomised controlled trial; SLE, systemic lupus erythematosus; SLR, systematic literature review; SpA, spondyloarthritis.

months and minimally further increased at 12 months. In a non-randomised study,²⁰ RA patients using an information/education website were not more adherent to their treatment than non-users.

Behavioural interventions

We only found one RCT evaluating a behavioural intervention.²¹ This study assessed the effects of cellular text messaging reminders on adherence to HCQ in patients with SLE and was negative.

In a prospective cohort study,²² investigators looked at the use of medication reminders such as pill containers, calendars or diaries in patients with RA. They found a positive association between using those reminders and a good adherence to treatment especially in situations with a high risk to forget to take the treatment: while away from home, when busy and when running out of pills (table 1).

Cognitive behavioural interventions

We only found one positive study on a cognitive behavioural intervention,²³ a RCT in which patients allocated

to the intervention arm received a cognitive behavioural therapy within 6 months, consisting in total 10 biweekly, 1 hour sessions and 1 final booster session scheduled 4 weeks later and were compared to a control group of patients who received usual care. This intervention was not systematic but targeted on patients being considered at high psychosocial risk. The cognitive behavioural therapy consisted of individual treatment with two of the four possible treatment modules that targeted the most frequently experienced problems with which patients with RA have to cope: pain and functional disability, fatigue, negative mood and social relationships. Adherence to RA medications significantly increased in the cognitive behavioural therapy group at 12 months follow-up assessment while adherence tended to decrease between baseline and follow-up visit in the control condition.

However, two others RCTs showed negative results.^{24 25} In both studies, non-adherent patients with RA using DMARDs were randomly allocated to an intervention arm (motivational interviewing-guided group sessions)

or to a control arm. These two studies did not demonstrate superiority of cognitive behavioural therapy by motivational interviewing over usual care to improve medication adherence. In a non-randomised study in RA and SLE,²⁶ motivational interviewing by phone every 2–4 weeks did not enhance medication adherence at 6 months (table 1).

Multicomponent interventions

No RCT evaluating multicomponent interventions was selected. In a prospective cohort study in patients with SLE,²⁷ HCQ blood levels were measured every 4 months and if patients had a low blood level (<500 ng/mL), they received an email asking not to forget to take their pills and were counselling on HCQ adherence at their next encounter. The proportion of adherent patients increased with each visit from 56% at first HCQ measure to 80% in those who had 3 visits or more traducing a benefit of this multicomponent intervention on adherence to HCQ in patients with SLE (table 1).

Other interventions

A pilot RCT²⁸ assessed the efficacy of an adapted low literacy medication guide and decision aid to improve medication adherence in patients with RA who belonged to vulnerable population. Although this shared decision-making process was acceptable and improved knowledge among these patients with RA, it did not increase medication adherence. In a cohort study of patients with RA or PsA who started a biological treatment,²⁹ a validated questionnaire was given to the patients in order to determine if the choice of treatment had been made with a shared decision-making process or not. Results at 6 months showed that patients who had been involved in a shared decision-making for biological therapy selection were more adherent to their biologic treatment than patients for whom treatment had been chosen only by the physician. However, a post-test study with a historical comparison group in patients with RA and SpA treated with DMARDs³⁰ did not demonstrate the efficacy of a web-based patient decision aid to improve medication adherence which was a secondary outcome in this study (table 1).

DISCUSSION

Medication adherence is a central problem in the management of chronic inflammatory rheumatic diseases. This systematic literature review highlights that educational interventions have been the most studied and have the highest level of evidence. However, it is worth noticing that an important heterogeneity exists between the studies across the modalities of these educational interventions: in some studies, interventions only consisted on an oral information on the disease and the treatment whereas in other studies interventions were designed as repeated individual or collective structured programs which certainly may have a different impact on patient adherence to treatment. Furthermore, the

actors of these educational interventions were different between the studies (physicians, pharmacists, nurses and so on). Cognitive-behavioural interventions have been proposed more recently. These interventions based on motivational interviewing are inspired from psychiatry. They have shown poor results in the selected studies with only one positive RCT and two negative RCTs. These negative results could be explained by the fact that the interventions were processed in group of patients who were all considered to be non-adherent to treatment. Indeed, motivational interviewing is usually an individual procedure. Nevertheless, these techniques seem to be of interest and need further prospective evaluation. They may be integrated into educational programs. As far as lupus is concerned, it has been shown that dosing HCQ blood levels and discussing the results of these levels with the patient, especially if they are low, was effective to improve adherence to HCQ whereas simple cellular text messaging reminders without HCQ dosing was not sufficient to enhance adherence of patients with SLE. Medication reminders such as pill containers, calendars or diaries have been studied in only one non-randomised study in RA. In this study, these behavioural interventions seemed to be useful, especially in situations at high risk of oversight. Finally, our review highlights the importance of shared decision-making when a physician wants to introduce a new treatment to his patient. It has been shown that when the decision is shared between the physician and the patient, medication adherence is higher. In our review, written or web-based medication decision aid did not help for medication adherence.

Results of our systematic literature review are in concordance with data published in other non-rheumatological chronic disorders such as type 2 diabetes in which medication adherence is particularly important. Indeed, in this metabolic disease, interventions which have been shown to improve medication adherence are multicomponent interventions with a great place for educational interventions.³¹

Our study has strengths and weaknesses. To our knowledge, this is the first systematic literature review on interventions to improve medication adherence in a large panel of chronic inflammatory rheumatic conditions. After reviewing 1325 publications, 22 studies had analysable data. This is due to the fact that many studies did not report the effect of an intervention on medication adherence. Moreover, a large number of studies we found did not treat on medication adherence but on retention rate which is not the same topic. Unfortunately, we could not calculate effect sizes and a good quality meta-analysis could not be made due to the heterogeneity of the designs of the studies. Despite we found only 13 RCTs, the majority of the non-randomised studies had a control group and we have thereby an idea of the effect of some interventions on medication adherence. However, the main disease studied was RA and there is a lack of evidence on the effect of such interventions on adherence in the other chronic rheumatism.

Despite the importance of medication adherence in clinical practice in the management of patients suffering from chronic inflammatory rheumatic disorders, evidence on interventions to improve medication adherence is scarce. Educational interventions have been evaluated in a few studies but these studies are heterogeneous and the results are unsatisfactory. These disappointing results might have several potential explanations: perhaps interventions are not targeting the right patients; perhaps the interventions are not sufficiently tailored. Perhaps also non-adherence, due to its multifactorial nature, is difficult to act on.^{32–34} Overall, non-pharmacological interventions pose specific methodological problems; thus, the mitigated results of trials should be interpreted with caution.³⁵ However, this systematic literature review points out the importance of the direct intervention between the healthcare providers at multiple levels in order to improve medication adherence. Indeed, all health professionals are involved in adherence. In particular, on top of rheumatologists, healthcare teams including nurses are important. Pharmacists will increasingly be involved as well. Advice by pharmacists on drug management has been shown to promote drug adherence, both in rheumatology and in other chronic disease settings.^{36–37} The role of pharmacists may vary of course according to the healthcare system. Furthermore, over the past years, e-health has taken on increasing importance. Patients seek information online and websites or apps might participate in promoting adherence.³⁸ Therefore, further good-quality RCTs are needed to better evaluate interventions to optimise medication adherence in chronic inflammatory rheumatic diseases.

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