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A systematic literature review of existing tools used to assess medication adherence in connective tissue diseases: the state of the art for the future development of co-designed measurement tools

S. Pirri[1], R. Talarico[2], D. Marinello[2], G. Turchetti[1], M. Mosca[2]

[1]*Institute of Management, Scuola Superiore Sant'Anna, Pisa;*
[2]*Rheumatology Unit, Azienda Ospedaliero Universitaria Pisana, Pisa*

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SUMMARY

Lack of medication adherence is frequent in chronic connective tissue diseases and is associated with poorer health outcomes, low quality of life and economic loss.

This research is based on a systematic literature search and aims to identify the surveys and tools used for the assessment of medication adherence in patients with connective tissue diseases (CTDs) and in particular the tools co-designed with patients.

A systematic literature review was performed in PubMed and Embase databases searching for studies concerning the application of surveys or tools designed for medication adherence assessment. A specific analysis was also performed to identify which of these existing tools were developed in co-design with patients affected by CTDs.

1958 references were identified, and 31 studies were finally included. Systemic lupus erythematosus was the most investigated disease, followed by the Behçet's disease. The tools used to assess adherence in CTDs were, in most cases, valid and useful. However, the results showed a certain degree of heterogeneity among the studies and the medication adherence assessment and measurement tools adopted, which were mostly based on self-reported questionnaire. No co-designed tools with patients were found.

Low- and non-adherence were explored in some CTDs with valid and useful tools, while other CTDs still need to be assessed. Therefore, more efforts should be made to better understand the specific reasons for the low- and non-adherence in CTDs patients.

Key words: *Literature review, medication adherence, connective tissue diseases, score, instruments, outcomes, co-design, questionnaires.*

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INTRODUCTION

Adherence has been defined as the *'extent to which a person's behavior (in terms of taking medications, following diets, or executing other lifestyle changes) corresponds with agreed recommendations from a health care provider'* (1).

Depending on the types of disease, many factors and variables may affect the complexity of managing a treatment regimen. Self-care instructions can range from relatively simple treatment plans, such as taking a medication daily for preventive purposes, to remarkably complex daily plans, like taking multiple medications, monitoring symptoms or side effects, or making deep lifestyle changes like diets, daily exercise and other behavioral adjustments (2).

The lack of medication adherence leads to poorer health outcomes for the patients, which affect their quality of life, cause economic loss for the healthcare system and trigger uncertainty for the healthcare prescribers in dealing with the disease treatment (3, 4).

Despite the recognized harmful impact of non-adherence, the rate of patients who do not comply with their treatment regimens is still around 50% in most chronic conditions (5, 6).

Corresponding author:
Salvatore Pirri
Institute of Management,
Scuola Superiore Sant'Anna
Via Santa Cecilia, 3 - 56127 Pisa
E-mail: s.pirri@santannapisa.it

Over the last few decades, many approaches to measuring the magnitude of this complex issue were explored. However, healthcare professionals and researchers still have very little guidance on how to select the most suitable measurements to understand the mechanisms leading to non-adherence to treatment (7).

Undirect measurements like surveys and self-reported assessments are the most common methods used to rate adherence (8). Self-reported tools have the advantage of being practical, flexible, low cost and able to receive quick feedbacks thanks to their ease-of-use, as for example they can be shared through online assessments, paper questionnaires, interviews, etc. This has contributed to making them popular in many clinical settings (9).

However, in addition to the presence of recall biases, a big drawback of undirected measurements is that patients tend not to be completely reliable on reporting the real adherence rate (social desirability bias). This often happens because patients are concerned about generating negative opinions about them, so they tend to give answers that are considered more socially acceptable and in accordance with the expectations of health professionals (10).

Since the 1970s, collaboration with end-users from the very early stages of the design of a new service or a new product has been considered a consolidated approach in many industries (11). Despite this well-known strategy, the actual application of this kind of marketing approach is still little known in many healthcare domains (12). Nevertheless, a recent study showed how patient's experience data are positively associated with patient safety and clinical effectiveness (13). It is clear that patients' involvement in co-designing health-related tools and services may have a concrete positive impact, especially when all the stakeholders involved are mutually engaged. This approach could be extremely valuable in identifying the barriers and limitations causing low- and no-adherence in patients (14). This is particularly true in autoimmune rheumatic diseases and connective tissue and musculoskeletal diseases, such as systemic lupus erythematosus (SLE), Sjögren's syndrome or Ehlers-Danlos syndrome, in which the lack of medication adherence is also an issue (15, 16).

Connective tissue and musculoskeletal diseases (CTDs) encompass a considerable number of diseases and syndromes, including rare connective tissue diseases (systemic sclerosis, mixed connective tissue disease, inflammatory idiopathic myopathies, undifferentiated connective tissue diseases, anti-phospholipid syndrome), and complex connective tissue diseases (systemic lupus erythematosus, Sjögren's syndrome).

The extensive variability of the clinical pictures among different patients and also in the

Table I - MeSH terms search query for PubMed and EMBASE.

("Treatment Adherence and Compliance"[Mesh] OR "Medication Adherence"[Mesh] OR "Patient Compliance"[Mesh]) AND ("Mixed Connective Tissue Disease"[Mesh] OR "Connective Tissue Diseases"[Mesh] OR "Undifferentiated Connective Tissue Diseases"[Mesh] OR "Lupus Erythematosus, Systemic"[Mesh] OR "Sjogren's Syndrome"[Mesh] OR "Ehlers-Danlos Syndrome"[Mesh] OR "Polychondritis, Relapsing"[Mesh] OR "Antiphospholipid Syndrome"[Mesh] OR "Immunoglobulin G4-Related Disease"[Mesh] OR "Scleroderma, Systemic"[Mesh] OR "Behçet's Disease"[Mesh] OR "Scleroderma, Diffuse"[Mesh] OR "Polymyositis"[Mesh] OR "Dermatomyositis"[Mesh]) NOT ("Arthritis, Juvenile"[Mesh] OR "Arthritis, Rheumatoid"[Mesh] OR "Rheumatoid Arthritis, Systemic Juvenile" [Supplementary Concept])	PubMed search query: 946 articles
'treatment adherence and compliance'/exp AND ('mixed connective tissue disease'/exp OR 'mixed connective tissue disease' OR 'connective tissue diseases'/exp OR 'connective tissue diseases' OR 'undifferentiated connective tissue diseases'/exp OR 'undifferentiated connective tissue diseases' OR 'lupus erythematosus, systemic'/exp OR 'lupus erythematosus, systemic' OR 'sjogren/s syndrome'/exp OR 'sjogren syndrome' OR 'ehlers-danlos syndrome'/exp OR 'ehlers-danlos syndrome' OR 'polychondritis, relapsing'/exp OR 'polychondritis, relapsing' OR 'antiphospholipid syndrome'/exp OR 'behçet disease'/exp OR 'antiphospholipid syndrome' OR 'immunoglobulin g4-related disease'/exp OR 'immunoglobulin g4-related disease' OR 'scleroderma, systemic'/exp OR 'scleroderma, systemic' OR 'scleroderma, diffuse'/exp OR 'scleroderma, diffuse' OR 'polymyositis'/exp OR 'polymyositis' OR 'dermatomyositis'/exp OR 'dermatomyositis') NOT ('arthritis, juvenile'/exp OR 'arthritis, juvenile' OR 'arthritis, rheumatoid'/exp OR 'arthritis, rheumatoid' OR 'rheumatoid arthritis, systemic juvenile')	EMBASE search query: 1012 articles

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same patients over time represents a huge clinical challenge in the management of CTDs. This variability is related to different factors, such as the clinical manifestations of the diseases, the fluctuation between remission and exacerbation over time, the coexistence of manifestations related to irreversible damage, the occurrence of comorbidities and drug toxicities and the patient's related quality of life. In order to overcome this significant complexity, an interdisciplinary approach is absolutely crucial for the diagnosis and management of CTDs.

Such heterogeneous group of rare and complex connective conditions, which share some common immunopathogenic mechanisms, makes it complex for healthcare professionals to deal effectively with the treatment plan.

The main objectives of this systematic literature search were:

1) to identify, in the published literature, tools developed to measure and/or assess medication adherence in CTDs patients;
2) to explore whether the existing tools used to measure and/or assess medication adherence were developed in co-design with CTDs patients.

MATERIALS AND METHODS

We performed a systematic literature review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (17). The literature search was carried out in PubMed and EMBASE academic databases without any limitation in terms of dates. All the available publications until the 12th May 2020 were considered. The following MeSH terms were employed as search queries (Table I).

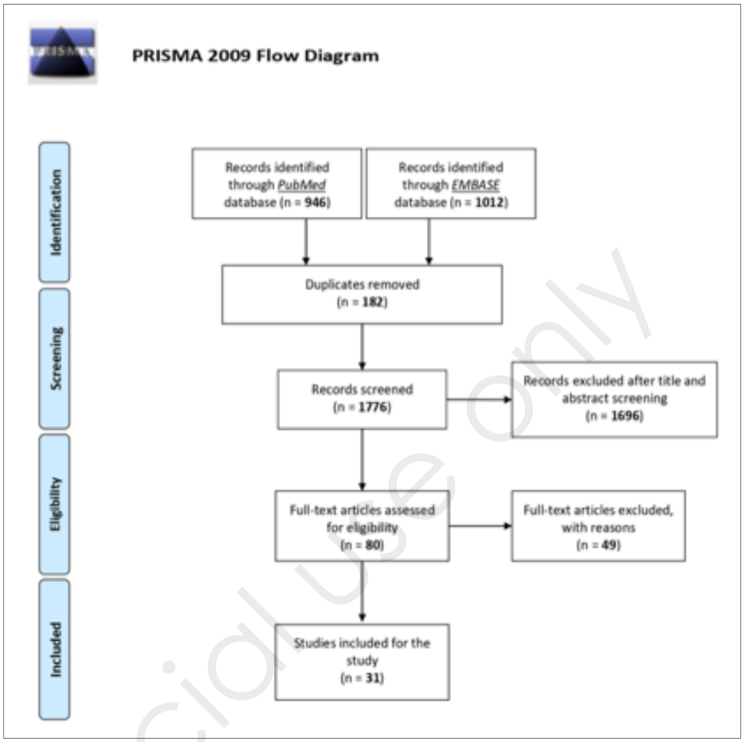

Figure 1 - PRISMA flow-chart.

Table II - Selection criteria for studies eligibility.

Inclusion criteria:
- Observational and experimental studies that report data on the adherence through surveys evaluating adherence, persistence, discontinuation of CTDs patients;
- Studies including adult patients (≥18 years old);
- Language: English;
- Peer-reviewed and full-text article available;
- *CTD diseases considered were mixed connective tissue disease, connective tissue diseases, undifferentiated connective tissue diseases, systemic lupus erythematosus, Sjögren's syndrome, Ehlers-Danlos syndrome, Behçet's disease, relapsing polychondritis, Antiphospholipid syndrome, IgG4-related disease, systemic sclerosis, polymyositis, dermatomyositis.*

Exclusion criteria:
- Studies that did not evaluate adherence, persistence, discontinuation in a clear statement;
- Studies that did not consider surveys or co-design methods with patients;
- Studies performed on other diseases than CTDs;
- Studies that did not employ surveys, chart medical records or registries;
- Studies with undefined data source;
- Papers not available in English.

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To achieve the study objectives and ensure an accurate result a blind check of the articles retrieved in the literature was performed independently by two authors, SP and RT, according to the inclusion and exclusion criteria shown in Table II. Disagreement between the two reviews was resolved by consensus with the other authors.

RESULTS

The results of the PRISMA flowchart are shown in Figure 1. A total number of 1958 studies, 946 in PubMed and 1012 in EMBASE, were identified in the databases. After removing the duplicates, 1776 articles were screened, checking titles and abstracts according to the selection criteria (Table II). Eighty articles were screened as full-text assessment, of which 31 studies were selected for this systematic literature review.

Systemic lupus erythematosus was the most investigated disease in terms of treatment adherence with 26 studies (83%). Three studies (9%) were conducted in Behçet's disease patients, while two studies were focused on systemic sclerosis. A summary of the results of the selected studies is presented in Table III (18-48).

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Table III - Summary of the selected studies. Studies are ordered by publication year and the alphabetic authors name order.

Authors	Title	Journal	Year	Disease	No. of patients	Tools/method	Adherence rate (%)
Du X, Chen H, Zhuang Y, Zhao Q, Shen B. (18)	Medication Adherence in Chinese Patients with Systemic Lupus Erythematosus	J Clin Rheumatol	2020	Systemic lupus erythematosus (SLE)	144	Compliance questionnaire rheumatology (cqr)	43%
E Hachulla, N LeGouellec, D Launay, Marie-Hélène Balquet, et al. (19)	Adherence to hydroxychloroquine in patients with systemic lupus: contrasting results and weak correlation between assessment tools	Joint Bone Spine	2020	Systemic lupus erythematosus (SLE)	145	Medication Adherence Self-Report Inventory (MASRI) and Morisky Medication Adherence Scales (MMAS-8)	63%
Harry O, Crosby LE, Mara C, Ting T V, Huggins JL, Modi AC. (20)	Feasibility and acceptability of an innovative adherence intervention for young adults with childhood-onset systemic Lupus Erythematosus	Pediatr Rheumatol	2020	Systemic lupus erythematosus (SLE)	19	Medication Adherence Self-Report Inventory (MASRI)	NA
Ali AY, Abdelaziz TS, Essameldin M. (21)	The prevalence and causes non-adherence to immunosuppressive medications in patients with lupus nephritis flares	Curr Rheumatol Rev	2019	Systemic lupus erythematosus (SLE)	104	Morisky Medication Adherence Scales (MMAS-8)	35%
Brijs J, Arat S, Westhovens R, Lenaerts JL, De Langhe E. (22)	Treatment adherence in systemic sclerosis: A cross-sectional study	Musculoskeletal Care	2019	Systemic sclerosis	66	Compliance questionnaire rheumatology (cqr)	28%
Clowse MEB, Eudy AM, Revels J, Neil L, Sanders GD. (23)	Provider perceptions on the management of lupus during pregnancy: barriers to improved care	Lupus	2019	Lupus during pregnancy	0	PRECEDE/ PROCEED framework	NA
Amalia R, Sasongko H, Kundarto W, Niruri R. (24)	The analysis of the factors affecting medication adherence in patient with SLE (Systemic Lupus Erythematosus) at Yayasan Tittari Griya Kupu Solo	Indian J Public Heal Res Dev	2019	Systemic lupus erythematosus (SLE)	41	Morisky green levine scale (mgls)	36%
Sun K, Eudy AM, Rogers JL, Criscione-Schreiber LG, Doss J, Sadun RE, et al. (25)	197 Racial disparities in lupus medication adherence	Lupus Sci Med	2019	Systemic lupus erythematosus (SLE)	84	Medication Adherence Self-Report Inventory (MASRI)	50%-64%

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Authors	Title	Journal	Year	Disease	No. of patients	Tools/method	Adherence rate (%)
Wallace DJ, Tse K, Hanrahan L, Davies R, Petri MA. (26)	Hydroxychloroquine usage in US patients, their experiences of tolerability and adherence, and implications for treatment: Survey results from 3127 patients with SLE conducted by the Lupus Foundation of America	Lupus Sci Med	2019	Systemic lupus erythematosus (SLE)	2783	HCQ dosage questionnaire	NA
Zayed HS, Medhat BM, Seif EM. (27)	Evaluation of treatment adherence in patients with Behçet's disease: its relation to disease manifestations, patients' beliefs about medications, and quality of life	Clin Rheumatol	2019	Behçet's disease (BD)	67	Compliance questionnaire of rheumatology (CQR)	22%
Khabbazi A, Karkon Shayan F, Ghojazadeh M, Kavandi H, Hajialiloo M, Esalat Manesh K, et al. (28)	Adherence to treatment in patients with Behçet's disease	Int J Rheum Dis	2018	Behçet's disease (BD)	137	Self-reported questionnaire	50%
Georgopoulou S, Nel L, Sangle S, Robson M, D'Cruz DP. (29)	Physician-patient interaction and medication adherence in lupus nephritis	Rheumatology	2018	Systemic lupus erythematosus (SLE)	98	Self-reported questionnaire	NA
Costedoat-Chalumeau N, Houssiau F, Izmirly P, Le Guern V, Navarra S, Jolly M, et al. (30)	A Prospective International Study on Adherence to Treatment in 305 Patients with Flaring SLE: Assessment by Drug Levels and Self-Administered Questionnaires	Clin Pharmacol Ther	2018	Systemic lupus erythematosus (SLE)	305	Medication Adherence Self-Report Inventory (MASRI) & Morisky Medication Adherence Scales (MMAS-8)	61%
Iudici M, Pantano I, Fasano S, Pierro L, Charlier B, Pingeon M, et al. (31)	Health status and concomitant prescription of immunosuppressants are risk factors for hydroxychloroquine non-adherence in systemic lupus patients with prolonged inactive disease	Lupus	2018	Systemic lupus erythematosus (SLE)	83	HCQ dosage questionnaire and blood samples	71%
Alsowaida N, Alrasheed M, Mayet A, Alsuwaida A, Omair MA. (32)	Medication adherence, depression and disease activity among patients with systemic lupus erythematosus	Lupus	2018	Systemic lupus erythematosus (SLE)	140	Morisky medication adherence scales (mmas-4)	38%
Kenneth Johnsen, Meenakshi Jolly, Narender Annapureddy. (33)	Health related quality of life in lupus: Self-management-a modifiable predictor	ACR/ARHP Annual Meeting	2017	Systemic lupus erythematosus (SLE)	50	Medication Adherence Self-Report Inventory (MASRI)	NA
Alexandra Perel-Winkler, Kayla Neville, Samantha Nguyen, Miya Okado, James Miceli, Jon T. Giles, Anca Askanase. (34)	Low health literacy does not impact adherence to hydroxychloroquine in patients with systemic lupus	ACR/ARHP Annual Meeting	2017	Systemic lupus erythematosus (SLE)	67	Self-reported questionnaire	NA
Farinha F, Freitas F, Águeda A, Cunha I, Barcelos A. (35)	Concerns of patients with systemic lupus erythematosus and adherence to therapy - a qualitative study	Patient Prefer Adherence	2017	Systemic lupus erythematosus (SLE)	15	Semi-structured face-to-face interviews	NA
Cinar M, Cinar FI, Acikel C, Yilmaz S, Çakar M, Horne R, et al. (36)	Reliability and validity of the Turkish translation of the beliefs about medicines questionnaire (BMQ-T) in patients with Behçet's disease	Clin Exp Rheumatol	2016	Behçet's disease (BD)	125	Beliefs about Medicines Questionnaire (BMQ)	NA
Flower C, Hambleton I, Campbell M. (37)	The Effect of Psychosocial and Neuropsychiatric Factors on Medication Adherence in a Cohort of Women with Systemic Lupus Erythematosus	J Clin Rheumatol	2016	Systemic lupus erythematosus (SLE)	106	Morisky medication adherence scales (mmas-4)	60%

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Authors	Title	Journal	Year	Disease	No. of patients	Tools/method	Adherence rate (%)
Cristina Drenkard, Sonia Mathew, Gaobin Bao. S. Sam Lim. (38)	Depression Is a Risk Factor for Low Treatment Adherence in African American People with Systemic Lupus Erythematosus	ACR/ARHP Annual Meeting	2016	Systemic lupus erythematosus (SLE)	326	Morisky Medication Adherence Scales (MMAS-8)	46%
Singh JA, Qu H, Yazdany J, Chatham W, Dall'Era M, Shewchuk RM. (39)	Barriers to medication decision making in women with lupus nephritis: A formative study using nominal group technique	J Rheumatol	2015	Systemic lupus erythematosus (SLE)	51	Nominal group technique (NGT)	NA
Hale ED, Radvanski DC, Hassett AL. (40)	The man-in-the-moon face: a qualitative study of body image, self-image and medication use in systemic lupus erythematosus	Rheumatology	2015	Systemic lupus erythematosus (SLE)	15	Semi-structured face-to-face interviews	NA
Hromadkova L, Soukup T, Cermakova E, Vlcek J. (41)	Drug compliance in patients with systemic scleroderma	Clin Rheumatol	2012	Systemic sclerosis	41	Compliance questionnaire rheumatology (cqr)	75%
Daleboudt GMN, Broadbent E, McQueen F, Kaptein AA, et al. (42)	Intentional and unintentional treatment nonadherence in patients with systemic lupus erythematosus	Arthritis Care Res	2011	Systemic lupus erythematosus (SLE)	106	Self-reported questionnaire	86%
Duvdevany I, Cohen M, Minsker-Valtzer A, Lorber M. (43)	Psychological correlates of adherence to self-care, disease activity and functioning in persons with systemic lupus erythematosus	Lupus	2011	Systemic lupus erythematosus (SLE)	100	Self-reported questionnaire	NA
Bennett JK, Fuertes JN, Keitel M, Phillips R, et al. (44)	The role of patient attachment and working alliance on patient adherence, satisfaction, and health-related quality of life in lupus treatment	Patient Educ Couns	2011	Systemic lupus erythematosus (SLE)	193	General adherence inventory	NA
Chambers SA, Raine R, Rahman A, Isenberg D. (45)	Why do patients with systemic lupus erythematosus take or fail to take their prescribed medications? A qualitative study in a UK cohort	Rheumatology	2009	Systemic lupus erythematosus (SLE)	315	Self-reported questionnaire	NA
Chambers S, Raine R, Rahman A, Hagley K, De Ceulaer K, Isenberg D. (46)	Factors influencing adherence to medications in a group of patients with systemic lupus erythematosus in Jamaica	Lupus	2008	Systemic lupus erythematosus (SLE)	75	Self-reported questionnaire	56%
Koneru S, Kocharla L, Higgins GC, Ware A, Passo MH, Farhey YD, et al. (47)	Adherence to medications in systemic lupus erythematosus	J Clin Rheumatol	2008	Systemic lupus erythematosus (SLE)	63	Medication Adherence Self-Report Inventory (MASRI)	61%
Garcia Popa-Lisseanu, Greisinger M, Richardson A, et al. (48)	Determinants of treatment adherence in ethnically diverse, economically disadvantaged patients with rheumatic disease	J Rheumatol	2005	Systemic lupus erythematosus (SLE)	22	Focus groups	NA

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Self-reported measurements, such as in interviews, self-reported questionnaires and focus groups in which patients provided information about medication they were taking, emerged as the most practical and common approaches to measure the adherence rate in CTDs (28, 29, 34, 35, 39, 40, 42, 43, 45, 46, 48). In particular, seven studies developed a tailored self-reported questionnaire to assess medication adherence. For instance, Chambers et al. (46) developed their own qualitative study using interviews and questionnaires covering socio-demographic information such as: age, sex, ethnic group, employment status, religion and treatment details. The questionnaire also allowed the authors to estimate, by asking respondents, the percentage of days related to the previous six months in which patients took all their prescribed medicines. These tools revealed that the main reasons for poor medication adherence were the cost and the setting-related availability of the medication. Patient interviews are generally considered practical low-cost tools that, under certain conditions, can explore the reasons behind behaviors of patient in taking medication, thus providing explanations for any difficulties in following their treatment regimens. Even if the questionnaires address specific aspects related to condition factors, which cannot be explored with other types of general medication adherence questionnaires, none of the seven questionnaires can be considered a gold standard approach to assess medication adherence. Moreover, none of them was developed in

Table IV - Summary table of questionnaire domain exploration.

Questionnaire/ tool	Number of questions	Domain	Advantages	Limitations
Brief Medication Questionnaire (BMQ)	9 questions	The Brief Medication Questionnaire (BMQ) is composed of 9-item, can explore both patients taking behavior and barriers to adherence. Includes 5-item for regimen screening, 2-item for belief screen about drug effects, and 2-item recall difficulties in remembering. One of the main advantages is that it can evaluate multi-drug regimens. However, it is time-consuming compared with other questionnaires, therefore it is difficult to use at the point of care.	It evaluates multi-drug regimens. It explores patients taking behavior and barriers to adherence.	Time-consuming Complicated scoring system
Compliance questionnaire rheumatology (CQR)	19 questions	The CQR is a patient-oriented questionnaire rheumatology-specific tool that measures patient adherence to drug regimens, detects factors that contribute to sub-optimal patient compliance. When used in conjunction with specialized psychosocial measures, it provides information such as the barriers to taking medication.	It encourages psychometric properties. Indication of the social or cognitive reasons behind non-adherence.	Time-consuming. Long series of questions. The discriminant ability does not correlate well in either compliance or correct dosing.
Medication Adherence Self-Report Inventory (MASRI)	12 questions	The Medication Adherence Self-Report Inventory (MASRI) is a self-administered questionnaire, easily manageable in the clinical setting. It offers an accurate measurement of adherence to the drug therapy in systemic lupus erythematosus (SLE). MASRI addresses two broad themes: the amount of medication taken and the timing of the doses. However, MASRI does not allow the assessment of medication overuse.	Easy and manageable in clinical setting. Suitable for systemic lupus erythematosus.	Time-consuming. Not consider medication overuse.
Morisky Medication Adherence Scale (MMAS-8)	8 questions	The Morisky Medication Adherence Scale (MMAS-8) developed from the original four-item MGLS is the most used questionnaire for medication adherence assessment. It identifies reasons for medication non-adherence and has better internal consistency. Nevertheless, like the MGLS, MMAS-8 has disadvantages, such as capturing only a few factors associated with non-adherence, thus providing limited information to develop interventions targeting non-adherence.	It captures the behaviour of patients in taking medications. High internal consistency.	Expensive Limited ability to capture non-adherence reasons.
Morisky Medication Adherence Scale (MMAS-4)	4 questions	Four dichotomous items compose the 4-item Morisky Medication Adherence Scale (MMAS-4), offering an easy and practical application in the clinical setting. Like in the MMAS-8, it is able to capture the medication taking behaviour of patients, but not properly assess the reasons or predictors of medication adherence.	High validity and reliability. Short questionnaire.	Expensive. Limited ability to capture non-adherence reasons.
Morisky green levine scale (mgls)	4 questions	Designed as a four-item scale, the Morisky Green and Levine (MGLS) Medication Adherence Scale is a dichotomous questionnaire based on "yes" or "no" response categories. MGLS can address barriers to medication-taking and permit the health care provider to reinforce positive adherence behaviors. However, in some studies MGLS has shown poor consistency when used in an elderly population. In particular, as a single measure of adherence it does not show an acceptable level of reliability.	Short questionnaire. Easily integrated into the medical visit	It fails to identify partial adherence. Patient's desirability bias It lacks consistency

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co-design with patients or with any other stakeholder. In addition, the drawback of this approach is the relatively poor sensitivity and consistency of the questionnaire leading to possible skewed results (49, 50).

The second set of tools was identified, relying on structured and validated questionnaires. The Medication Adherence Self-Report Inventory (MASRI) (51), the 4-item (52) and 8-item (53) Morisky Medication Adherence Scale (MMAS), and the Brief Medication Questionnaire (BMQ) (54), were identified as the most used and structured set of tools found in our results. These tools apply cut-off values or rank the degree of the medication adherence rate. Such approaches can minimize the limitations of other self-reported methods by standardizing the measurement and increasing the validation consistency. These questionnaires are often validated with statistical tests and combined with other subjective or objective measures, thus improving the consistency of the results (55). The MASRI questionnaire was adopted in five papers (20, 25, 30, 33, 47) and all studies explored the adherence rate in SLE. The CQR was used in four publications (18, 22, 27, 41 not only in lupus, but also in systemic sclerosis and Behçet's disease, given it is specific for rheumatological disorders. The eight items of the MMAS were used in three papers (21, 30, 38), while the version with 4 items was used in two more papers (32, 37). It is important to highlight that the 8-item MMAS was particularly valuable in these studies, as it makes it possible to recognize whether the causes of non-adherence are intentional or non-intentional, demonstrating the added value of this tool also regarding patient beliefs about medicine. A tool for assessing patient beliefs about medicine is the BMQ, used by Çinar et al. (36) who validated its Turkish translation.

Alternative tools with other tailored characteristics, such as exploring specific factors related to the disease(s) or treatments, were adopted in three studies (26, 31, 44). These tools can be considered valuable alternatives to investigate specific variables that may not be captured with standard tools, even if further validation might be useful to enhance consistency and ensure their implementation.

An interesting research was recently published regarding adherence assessment of SLE patients in France (19), which showed how the combination of different tools with direct and indirect measurements can provide an overall estimation of the magnitude and reasons behind non-adherence. Specifically, the authors reported that the combination of blood hydroxychloroquine concentration with MASRI and MMAS-8 may help to better identify non-adherence in SLE.

The ideal medication adherence assessment tool should have a user-friendly design, be easy and practical to use in any clinical settings and offer high reliability and consistency. However, this is not yet reality, since so far no tool can meet all these standards at the same time and each tool has its own advantages and drawbacks.

In summary, Table IV reports the advantages, limitations, and specific domain of each of the main questionnaires showing at a glance all the differences across the various medication adherence tools identified.

DISCUSSION

Medication adherence is a pivotal problem in the management of connective tissue diseases. The results of this study demonstrated the existence of valid tools aimed at measuring the medication adherence rate. Since the ideal measurement tool should be as much flexible, reliable, and practical as possible for the clinical setting as well as for the patient, the existing tools can be considered appropriate to measure the adherence rate in CTDs. However, only a few CTDs have been extensively studied so far, in particular, SLE, Behçet's disease and systemic sclerosis.

Across all the included studies, a wide range of tools and methods were found to assess medication adherence. Each tool has pros and cons and explores important dimensions to mitigate patient non-adherence barriers. Although the included studies met standards for describing rationale

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and methods, existing studies are not yet involving patients and their representatives in the co-design phase during the methodological development. Such an approach, in our opinion, can provide a significant added value in identifying the boundaries of non-adherence at the patient level, and the associated modifiable factors.

The MMAS in both versions, (MMAS-4) and (MMAS-8), is a well-known tool used to measure adherence in patients with chronic conditions. The original version with four items developed by Morisky was quite innovative in capturing the fundamental reasons for non-adherence (56). The eight items (MMAS-8) version developed in 2008 improved the psychometric properties, increased sensitivity and specificity, as reported in several studies, and was translated into many languages (57). MMAS-8 is the most widely used self-reported measurement for medication adherence assessment. Another relevant tool is the MASRI, a concise self-administered tool composed of 12 items which can be easily administered in the clinical setting and is effective in SLE drug therapy assessment (58). Originally used in HIV therapy, the MASRI questionnaire has proven useful for adherence assessment in SLE, adopting a visual analogue scale (VAS) item which is known and massively used in rheumatologic settings to estimate a numeric value of the adherence rate (0-100%).

In addition, the CQR (59) is a validated tool for measuring adherence in rheumatic diseases. CQR can identify factors that contribute to sub-optimal adherence like social or cognitive factors. It was validated against the medication event monitoring system (eMEMs), which is an electronic cap fitted on standard drug bottles indicating the time and date on which the bottle was opened. The CQR questions were identified through focus groups and clinical expert opinions. Despite this tool has proven valuable, it can be difficult to apply routinely in some clinical settings, as it consists of 19 items (60).

Only a few studies explored the efficacy of educational interventions aimed at improving the adherence to treatment. These studies yielded some heterogeneous results that could encourage the implementation of projects which involve patients in the co-design of these interventions. As a matter of fact, evidence clearly suggests that the lack of patient engagement and confidence plays an important role (61). On the other side, motivation and support in meeting their needs with tools resulting from a co-design process (62) could increase patient confidence and knowledge in addressing such complex issues.

Many of the studies reported in this paper have used a combination of tools, including blood samples as a direct approach to explore medication adherence.

The provided evidence suggests clearly that a low medication adherence rate is a reality also among patients with CTDs, similarly to other chronic diseases. For this reason, one of the priorities that should be considered is the co-creation and organization of initiatives aiming to improve the relevance of adherence measurement and to promote patient education. For this purpose, existing tools could be reinforced with additional features aimed at exploring in greater detail the real reasons and barriers behind low- or non-adherence. The identification of these issues should be considered the basis for planning and implementing tailored actions and initiatives specifically aimed at improving medication adherence in CTDs. Since CTDs are heterogeneous and can include different phenotypes, the reasons behind low- and non-adherence can be really variable not only in the different diseases, but also in the different subsets of the same disease (*e.g.* low- or non-adherence related to disease remission is very different from low- or non-adherence due to being scared by possible adverse drug reactions). The development of additional tailored tools created in co-design with all the stakeholders involved in adherence management would be crucial to ensure that the various dimensions and barriers leading to low- and non-adherence can be identified and addressed in actions aimed at improving adherence in CTDs patients. This kind of approach is even more important in CTDs because the complexity

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of these diseases and the low number of patients cannot guarantee enough information for strong statistical assumptions (63).

CONCLUSIONS

Low- and non-adherence were explored in some CTDs with valid and useful tools, while other CTDs still need to be assessed. Therefore, more efforts should be focused on better understanding the specific reasons for the low- and adherence in CTDs patients. Moreover, additional tools should be developed in co-design with patients and other stakeholders in order to provide a comprehensive approach (64) to include the different types of dimensions, such as: beliefs, personal preference, social support, disease conditions and patient-doctor and patient-caregiver relationships. The limitations and barriers related to low- and non- adherence can be then addressed in specific co-designed initiatives that can increase adherence and, therefore, improve not only health outcomes, but also the quality of life of patients affected by CTDs.

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Disclosure
The authors declare no conflicts of interest.

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