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Research Article

# Assessment of medication adherence in patients with rare diseases: a systematic review

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## Abstract

**Background:** The study aims to critically analyze the scientific literature concerning methods for assessing medication adherence (MA), the factors that influence it, medication adherence-enhancing interventions (MAEIs), and the consequences of medication nonadherence (MNA) among rare diseases (RDs) patients.

**Methods:** Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a systematic search was conducted on PubMed's electronic database until 26 January 2024, regardless of the publication year or type. All identified articles were exported to Rayyan and Mendeley software tools to remove duplicate papers. Two authors independently reviewed the selected articles to determine their relevance to the inclusion and exclusion criteria. Articles that did not provide summarized reports of MA in patients with RD, did not have full text available, sufficient information in the abstract, or an English translation were excluded. One investigator entered the study data into the extraction table, and another verified it for accuracy and completeness. A protocol has been registered on the Open Science Framework platform. The risk of bias was assessed using the Mixed Methods Appraisal Tool and the Joanna Briggs Institute tools.

**Results:** Twenty-nine studies met the inclusion criteria, along with 20 additional studies from our previous published scoping review. MA among patients with RD exhibited considerable variability, with prevalent assessment measures including the Morisky Medication Adherence Scale (n = 6), questionnaires (n = 7), databases/registries (n = 5), and a combination thereof (n = 5). The most common factors associated with MNA were patient- and therapy-related. Notable risks of MNA included hospital admissions and disease worsening. Educating patients and considering their preferences were the most frequently used MAEIs.

**Conclusion:** Efforts are crucial to ensure the timely assessment, reporting, and enhancement of MA. The lack of a specific approach adopted via the national legal framework might be recognized as one of the main factors for neglecting MNA issues in this group of patients.

## Keywords

medication adherence-enhancing interventions, medication adherence-influencing factors, medication non-adherence, uncommon diseases

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PENSOFT

## Introduction

Rare diseases (RDs) are life-threatening or chronic debilitating diseases with low prevalence and high complexity. According to the European definition, a RD has a prevalence of no more than 5 per 10,000 people in the European Union (EU) or a disease that affects no more than one in 2,000 EU citizens (Moliner and Waligora 2017; Public Health 2022).

In addition to the nature and severity of the illness, accurate diagnosis, and timely intervention, medication adherence (MA) is a significant factor contributing to effective treatment. MA is the process by which patients take their medications as prescribed, composed of initiation (starting the prescribed medication intake), implementation (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose), and discontinuation (the cessation of medication intake for any reason(s)). Persistence is the duration between the first and last doses, prefacing discontinuation (Vrijens et al. 2012). MA is often expressed as a percentage between 0% and 100%, with a threshold of ≥ 80% indicating sufficient adherence (Baumgartner et al. 2018).

Chronic, prevalent diseases have been extensively studied, revealing a significant challenge with MA, with an average adherence rate of around 50% (Mathes et al. 2012). A recent report highlighted that the global average nonadherence rate among RD patients is 58–65% (Atlantis Health 2023). Nevertheless, there are even wider variations in some RDs due to the different aspects involved in the greater or lesser applicability of the treatment (García-Muñoz et al. 2023). However, monitoring MA among patients with RD is uncommon due to the limited availability of drug therapies (Pogue et al. 2018). Another crucial aspect to be concerned about is whether the patients observed suffer from a specific rare disease (fewer than 5 cases per 10,000 people) or a rare tumor (6 per 100,000 people per year). Comparing these two groups in terms of MA might be associated with challenges mainly due to the different prevalence scales, population sizes, and case distribution. Potential differences that might appear and influence adherence patterns are related to treatment modalities, disease burden and progression, access to treatment, and social and psychological factors (Geissler et al. 2015).

Medication nonadherence (MNA) is a global issue leading to significant health and economic consequences for patients and society. According to the World Health Organization (WHO 2003), the five main factors contributing to nonadherence are social and economic-related, healthcare system-related, disease-related, therapy-related, and patient-related factors. Its high prevalence and negative impact on clinical and financial outcomes indicate the necessity for guidance on assessing MNA and implementing strategies to overcome these effects (Ruppar et al. 2015). Improving the effectiveness of MA interventions could have a much greater impact on population health than improving specific medical treatments (Chaudri 2004). This impact encompasses not only prevalent chronic diseases but RDs as well.

This study aimed to critically analyze, consolidate, and provide an overview of the scientific literature concerning MA assessment methods, influencing factors, medication adherence-enhancing interventions (MAEIs), and the consequences of MNAs among patients with RD.

## Materials and methods

### Study protocol registration and reporting

The protocol was registered on the Open Science Framework platform on 12 December 2023 (https://osf.io/rykwt). This review's report followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines checklist (Suppl. material 1) (Page et al. 2021).

### Data sources and search strategy

The search for studies relevant to the research question was initiated in the PubMed scientific database between 01 December 2023 and 26 January 2024, regardless of the publication year or publication type. Boolean operators (AND, OR) and MeSH search strategies were used to identify relevant articles. The detailed search strategy can be found in Suppl. material 2. All identified articles were exported to the Rayyan systematic review application (https://rayyan.qcri.org/) and Mendeley Reference Management Software (https://www.mendeley.com/reference-management/reference-manager) to screen and remove duplicate papers. Two authors (IH, PP) reviewed the selected articles to determine their relevance to the inclusion and exclusion criteria and consolidated the evidence. In cases of disagreement, a third reviewer (MK) was consulted. A flow diagram was generated to systematize the data.

### Inclusion and exclusion criteria

Articles were included based on the following criteria: 1) written in English; 2) patients with RDs who had received or were currently receiving treatment for their primary condition; and 3) studies addressing the research questions and reporting data on MA. Studies were excluded if they 1) did not report MA, 2) did not provide summarized results, 3) did not cover patients with RD, or 4) did not have full text available or sufficient information in the abstract.

### Eligibility criteria

Our search was conducted using routine practice approaches to the literature searches such as PICO (Population, Intervention, Comparison, Outcomes):

- Population: Patients diagnosed with a RD (adults and children), who have received or currently receive therapy prescribed for their illness;
- Intervention: MA issues and predictors among patients with RDs;

- Comparison: Watchful waiting without any interventions for the assessment and/or improvement of MA in the selected group of patients;
- Outcome(s): The primary outcome measures are the type of methods for assessment of MA and corresponding levels of MA among the selected population after diagnosing and prescribing therapy. The secondary outcomes include (a) type of risk factors, barriers, and predictors of MNA; (b) types of MAEIs; (c) outcomes associated with MNA such as hospital readmission rate, worsening of the condition, death, increasing direct and indirect costs, and other relevant consequences.

## Methodological quality assessment

The methodological quality of all included studies was assessed using the Mixed Methods Appraisal Tool [MMAT] 2018, except for systematic reviews (SRs) (n = 4), for which the Joanna Briggs Institute (JBI) meta-aggregative approach was used (Aromataris et al. 2015; Quan et al. 2018). The MMAT is a checklist used to evaluate the quality of various study designs, including quantitative, qualitative, and mixed-methods studies, focusing on the latter. In our SR, we utilized the MMAT to assess how effectively the included studies addressed potential biases that could affect the interpretation of the results. IH evaluated all studies, while MK and PP assessed 20% of the studies each. The JBI critical appraisal tool, used to determine the quality of the included SRs, contains eleven questions with four rating choices (i.e., yes, no, unclear, not applicable) for each question. Two appraisers (IH and MK) subjected these studies to rigorous appraisal. Detailed quality appraisal information is presented in Suppl. materials 3, 4.

## Data extraction and synthesis

One investigator (IH) entered the study data into the extraction table, while a second investigator (MK) verified the information for accuracy and completeness. The following data were extracted: author, year, country of origin, type of study, RD, MA aspect (assessment, improvement, factors), and results and conclusions. The characteristics of the 49 included studies are presented in Suppl. material 5.

# Results

## Selection of articles

The initial search across PubMed identified 308 results. One duplicate sample was found and removed through the Rayyan and Mendeley platforms (n = 1). Then, 307 studies were screened by title and abstract, and 212 records were removed. Ninety-five records were retained for full-text review. Finally, 29 articles from the PubMed database were included for analysis. The 20 articles included from our previous review (a scoping review published in 2023 in the International Journal of Clinical Pharmacy (PCNE abstract number 576) (Kamusheva et al. 2023) remain highly relevant and provide foundational insights into MA. As rare disease research often evolves slowly due to limited patient populations and available treatment, these studies contribute critical data and context to the overall assessment of MA. Fig. 1 visualizes a PRISMA flowchart of the selection process.

## Quality of the included studies

The risk of bias assessment results for each of the 49 studies is reported in Suppl. materials 3, 4. All included papers, appraised with the MMAT tool, had clear research questions, and the collected data adequately addressed them. However, some studies indicated unclear reporting regarding sampling and bias. This was not considered a rational basis for their exclusion. The included SRs, appraised with the JBI tool, show clearly and explicitly stated review questions with appropriate inclusion criteria, search strategies, and sources used to search for studies.

## Description of included studies

The studies were published between 2001 and 2023, with most published in 2022 (n = 7) and 2021 (n = 8) (Fig. 2). Of the 49 included studies, 6 were conducted in the USA, 4 in Spain, 3 in France, Italy, Brazil, 2 in Japan, Turkey, Germany, and the United Kingdom (UK), and 1 each in China, Sweden, Denmark, Switzerland, and Bulgaria. Additionally, 6 studies were multicentered, and 11 were systematic/literature reviews or conducted via telephone or social media. The detailed study characteristics are presented in Suppl. material 5.

## Level of adherence and methods for assessment

Medication adherence rate was assessed using the Morisky Medication Adherence Scale (MMAS) in most of the selected studies (n = 6), as wide variability (21%–62.7%) was demonstrated among 2,165 patients with RD (Dwyer 2014; Dzemaili et al. 2017; Ivarsson et al. 2018; Vitturi et al. 2020; Karaca et al. 2022; García-Muñoz et al. 2023). Some studies (n = 5) used large databases and registries to assess MA in 4,244 patients (Farach et al. 2012; Johansen et al. 2016; Mehta et al. 2021; Oro-Ayude et al. 2022; Saito et al. 2022). Seven studies included questionnaires with various scales to determine MA levels. These studies involved 1462 patients, 223 physicians, and 22 caregivers (De Moerloose et al. 2008; Alexander et al. 2017; Vatier et al. 2019; Walburn et al. 2019; Aycan et al. 2021; Torregrosa Prats et al. 2021; Hollmen et al. 2023). Moreover, five studies used or described various approaches to measure MA (Uomo et al. 2001; Sultan et al. 2018; Kamusheva et al. 2020; González-Lamuño et al. 2021; Jacquelet et al. 2021). The MA rate of each study is reported in Table 1.

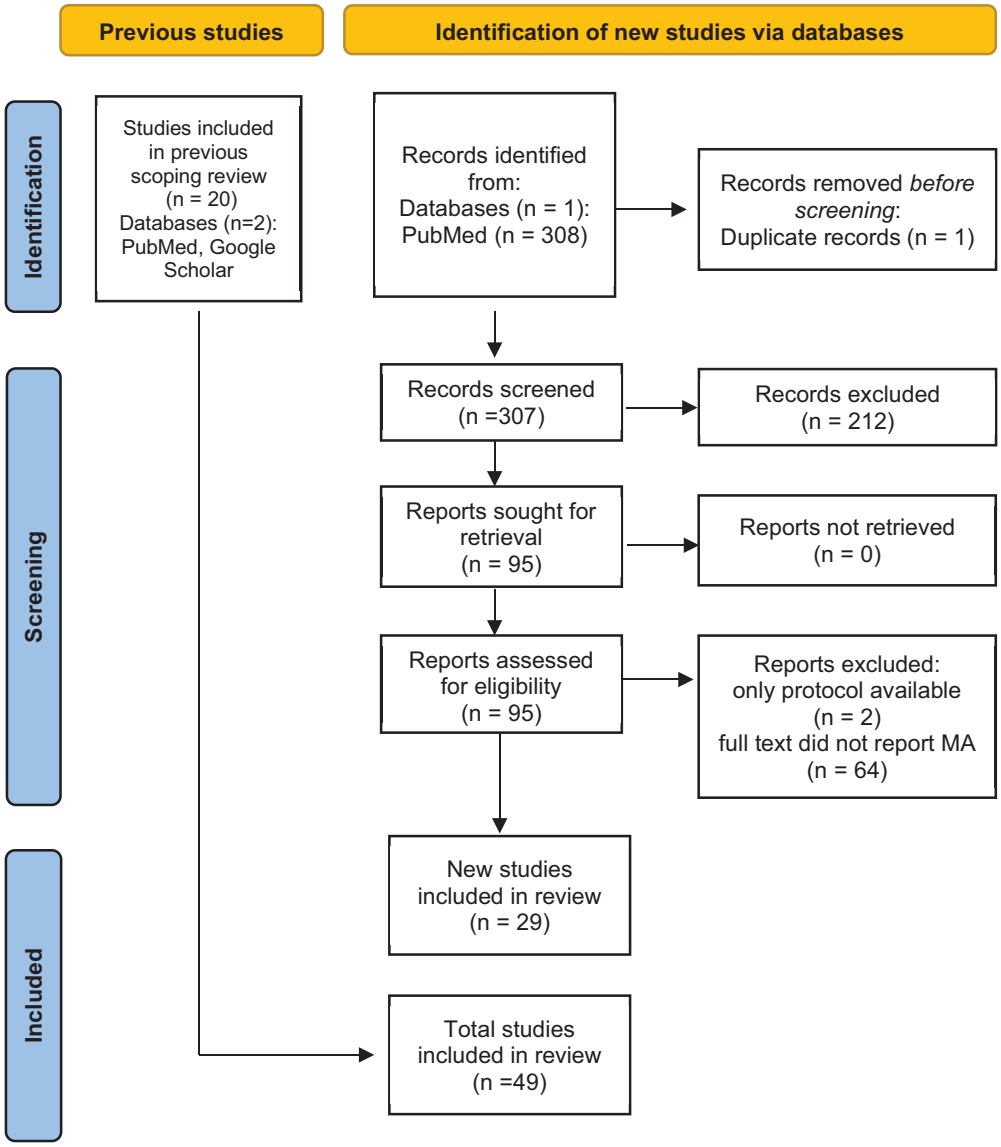


**Figure 1.** PRISMA flow diagram.

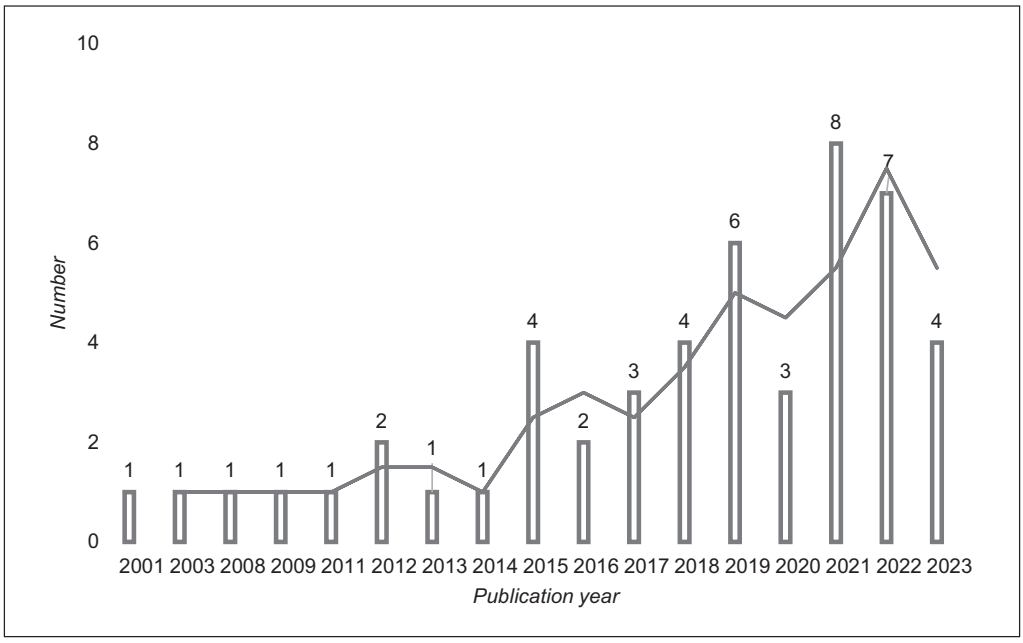


**Figure 2.** Number of publications by year 2001–2023.

**Table 1.** Methods for assessment of medication adherence and level of adherence.

| Author | Disease(s) | Number of participants | MA rate | Details for methods used |
|---|---|---|---|---|
| MMAS | | | | |
| **García-Muñoz et al. 2023** | MG, SCD, CHH, PAH, ALS, WD, FD, CF, Hemophilia A, myelodysplastic syndromes and β-thalassemia | 1.559 patients | 57.4% | MMAS-4; ;MMAS-8 |
| **Vitturi et al. 2020** | MG | 58 patients | 44.8% | MMAS-8 |
| **Ivarsson et al. 2018** | PAH and CTEPH | 325 patients | 57% | MMAS-8, BMQ-S scale and QLQ INFO25 multi-item scale |
| **Dzemaili et al. 2017** | CHH | 55 patients | 38.2% | MMAS-8 via patient-oriented social media (ex. Facebook, reconnect) |
| **Dwyer 2014** | CHH | 101 patients | 21% | MMAS-8 online |
| **Karaca et al. 2022** | FD | 67 patients | 62.7% | MMAS and MARS |
| Databases and registries | | | | |
| **Mehta et al. 2021** | CF | 2.548 patients | PDC ≥ 0.80 | National speciality pharmacy database |
| **Johansen et al. 2016** | HNSCC | 1.560 patients | 97.7% | Data from the Danish Head and Neck Cancer Group including radiotherapy records (total dose, fractionation and treatment duration) |
| **Saito et al. 2022** | ADPKD | 15 patients | The persistence rates, estimated by Kaplan- Meier analyses, at 12, 24, and 36 months were 70.8% (95% CI: 48.2–93.4), 46.5% (23.2–66.9), and 38.7% (16.4–60.8) | Shizouka Kokuho Database |
| **Oro-Ayude et al. 2022** | Genodermatoses | 9 patients | The correlation was greater than 89% | Recording patients' visits to the hospital pharmacy, correlating the number of planned and actual visits |
| **Farach et al. 2012** | CF | 112 patients | MPRm = 72%, with the worst adherence observed for tobramycin inhaled solution (60%) and the best adherence for oral azithromycin (84%) | Fully integrated pharmacy and electronic health record; calculating MPRm |
| Questionnaires with different scales | | | | |
| **Torregrosa Prats et al. 2021** | dRTA | 83 physicians | 4.4% reported excellent MA; 26.6% - a good or a very good MA rate | Ten-questions survey |
| **Walburn et al. 2019** | XP | 156 patients | 64.7% | Two subscale questionnaires (one to the face and one to the body) |
| **Hollmen et al. 2023** | IPF | 111 patients, 22 caregivers and 140 pulmonologists | 81% of the patients were adherent | An online survey |
| **Vatier et al. 2019** | Lipodystrophic syndromes | 20 patients | Excellent in 25% and acceptable in 50% of patients | Adherence Evaluation Test, TSQM*-vII |
| **De Moerloose et al. 2008** | Haemophilia A | 180 patients | 80–87% | Individual interviews with patients, haemophilia physicians and specialist nurses |
| **Alexander et al. 2017** | Vasculitis | 228 patients | High levels of MA (M = 4.3; SD = 0.69) | Online questionnaires at baseline and 3- month follow-up |
| **Aycan et al. 2021** | IGHD, MPHD, SGA, TS | 767 patients | 92% | Evaluating the number of missed injections and reports from the person administering daily GH injections in each visit to the physician |
| Combination of methods | | | | |
| **Jacquelet et al. 2021** | WD | 139 patients | High MA in 20.9% of patients, medium MA in 46.8% | MMAS and direct methods (blood levels of exchangeable copper and serum transaminases) |
| **Sultan et al. 2018** | Haemophilia and GH dysregulations | 8.597 patients | One in four to one in five patients (20%–25%) had issues with MA | Number of missed injections, used prescriptions filled or MPR, and data recorded by an electronic device (easypod) |
| **Uomo et al. 2001** | Hereditary chronic pancreatitis | 3 patients | Correct tablet intake was observed in 95.5% of the days of oral therapy | Number of tablets intake, clinical examinations, biochemical tests, abdominal ultrasound examinations and patient diaries |
| **González-Lamuño et al. 2021** | HT1 | 69 patients | 84% | Direct (quantifying blood levels of nitisinone (NTBC) and metabolic biomarkers of HT1 [tyrosine (Tyr), phenylalanine (Phe), and succinylacetone]) and indirect (Haynes–Sackett (or self- compliance) methods |
| **Kamusheva et al. 2020** | Acromegaly | 2.443 patients, 23 healthcare professionals and 126 endocrinologists | MPR (≥ 80%), 60.7%–92.1% according to the type of medicine used | MPR, number of injections, treatment duration, questionnaires, prescription-refill records, and counting missed doses |

**Abbreviations:** ADPKD, autosomal dominant polycystic kidney disease; ALS, amyotrophic lateral sclerosis; BMQ-S scale, beliefs about medicines questionnaire-specific scale; CF, cystic fibrosis; CHH, congenital hypogonadotropic hypogonadism; CTEPH, chronic thromboembolic pulmonary hypertension; dRTA, distal renal tubular acidosis; FD, fabry disease; HNSCC, squamous cell carcinoma of the head and neck; HT1, hereditary tyrosinemia type 1; IGHD, isolated growth hormone deficiency; IPF, idiopathic pulmonary fibrosis; MARS, medication adherence report scale; MG, myasthenia gravis; MMAS-4, Morisky medication adherence scale 4-item; MMAS-8, Morisky medication adherence scale 8-item; MPHD, multiple pituitary hormone deficiency; MPRm, modified medication possession ratio; N/A, not applicable; PAH, pulmonary arterial hypertension; PDC, proportion of days covered; PH1, primary hyperoxaluria type 1; QLQ-INFO25, quality of life questionnaire—information module; SCD, sickle cell disease; SGA, small for gestational age; TS, Turner syndrome; TSQM*- vII, the treatment satisfaction questionnaire for medication; WD, Wilson's disease; XP, xeroderma pigmentosum.

## Factors of adherence

The WHO categorizes factors leading to MNA into five main categories (World Health Organization 2003) as factors for MNA among RD patients, as shown in Fig. 3.

## Socioeconomic factors

Financial difficulties experienced by acromegaly patients were the reason for MNA in 89% of them (Kamusheva et al. 2021). A lack of health insurance was defined as a factor

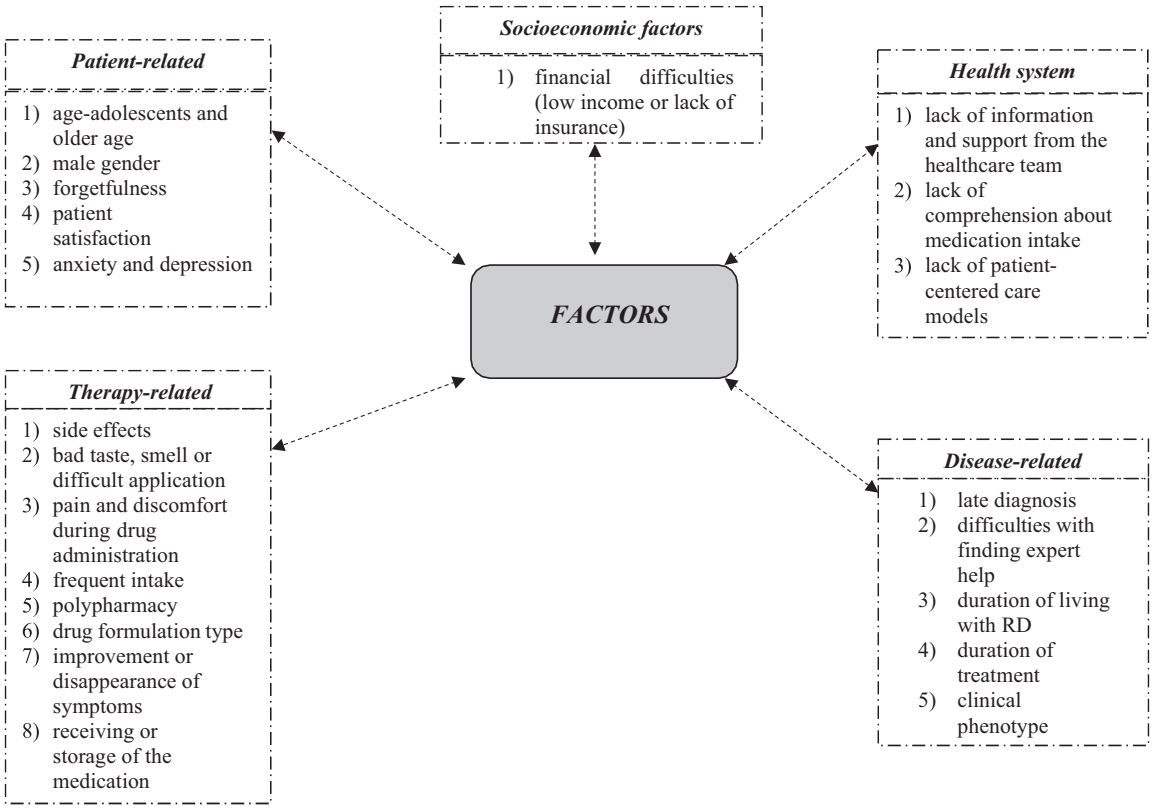


**Figure 3.** Factors leading to medication nonadherence among patients with rare diseases.

for refusing medication therapy, leading to multiple hospital readmissions (Shenoy et al. 2015).

## Healthcare team/health system factors

One identified factor contributing to MNA was a lack of systemic education and information about the disease among patients (Ivarsson et al. 2018; Vitturi et al. 2020; Hollmen et al. 2023). In one study, 52 out of 55 women with congenital hypogonadotropic hypogonadism (CHH) reported using the internet for information, with 46 involved in online communities and social media; 24 expressed a need for further information and support (Dzemaili et al. 2017).

## Disease-related factors

Late diagnosis, which causes a delay in finding expert help, was revealed as a reason for MNA in 13 out of 55 patients with CHH (Dzemaili et al. 2017). The time spent with the RD also affected MA; the longer the patients were treated, the less they adhered to therapy (Vitturi et al. 2020; Saito et al. 2022; Wang et al. 2022). The clinical phenotype can also lead to variations in the MA rate: patients suffering from Wilson's disease with high MA mainly have a neurological form (75.9%), while 26.7% of patients with an asymptomatic form have low MA (Jacquelet et al. 2021).

## Therapy-related factors

Side effects seem to be a common barrier to MA. Local side effects (pain, redness, skin infections or irritation, skin induration at the site of the injection) (Cappellini and Taher 2009; Vatier et al. 2019; Kamusheva et al. 2020; Pogna et al. 2021; Orso et al. 2022), as well as photosensitivity (Hollmen et al. 2023) and gastrointestinal issues (Pogna et al. 2021; Acquadro et al. 2022; Hollmen et al. 2023) are frequently mentioned. Drug toxicity (Costa et al. 2012) and concerns about potential adverse effects (Ivarsson et al. 2018) are also significant problems impacting adherence. For example, patients often discontinue their prescribed therapy without consulting their physician after experiencing side effects (Morrow 2019; Ueda et al. 2019).

Additionally, symptom improvement or disappearance can lead to treatment abandonment (De Moerloose et al. 2008; Kamusheva et al. 2021). The need for multiple daily or weekly medications and the large number of pills required have been associated with low MA rates, which are often below the 50% observed in other chronic diseases (Cappellini and Taher 2009; Thomson et al. 2011; Vitturi et al. 2020; Torregrosa Prats et al. 2021; Hollmen et al. 2023).

Other therapy-related issues were drug administration difficulties (Vatier et al. 2019; Kamusheva et al. 2020), the unavailability of medications on the market due to export issues, cold storage requirements, and increased distance to treatment centers (Aycan et al. 2021; Jacquelet et al. 2021; Hollmen et al. 2023).

## Patient-related factors

Forgetfulness regarding medication intake (De Moerloose et al. 2008; Jabbour et al. 2012; Orso et al. 2022; Hollmen et al. 2023), adolescence (De Moerloose et al. 2008;

Jabbour et al. 2012; Malik et al. 2015; Sultan et al. 2018; Medina and Román 2020; González-Lamuño et al. 2021), older age and male gender (Jabbour et al. 2012; Fentiman 2018; Wang et al. 2022; Hollmen et al. 2023), a low level of education (Sultan et al. 2018; Orso et al. 2022; Wang et al. 2022), and unpleasant organoleptic characteristics of the therapy (Oro-Ayude et al. 2022) were factors responsible for low MA. Moreover, anxiety and depressive episodes are prevalent in nonadherent patients (Jabbour et al. 2012; Dwyer 2014; Malik et al. 2015; Dzemaili et al. 2017; Jacquelet et al. 2021).

## Interventions for enhancing medication adherence (MAEI)

Educating patients about what to expect from their prescribed therapy, possible side effects, and how to prevent or manage them has emerged as one of the most important MAEIs (De Moerloose et al. 2008; Jabbour et al. 2012; Malik et al. 2015; Ivarsson et al. 2018; Kamusheva et al. 2021; Nguyen et al. 2023). Two of the studies highlighted that implementing practical guidelines is essential for managing the information patients receive about their therapy (Ivarsson et al. 2018; Kamusheva et al. 2021). Several studies have shown the significant impact of interventions and policies implemented by the healthcare system, like collaborative care models, involving close coordination between healthcare professionals (HCPs) and patients (De Moerloose et al. 2008; Van Groenendael et al. 2015; Morrow 2019; Vaisbich et al. 2019; Nguyen et al. 2023). Additionally, technological solutions, such as medication reminder apps, devices that permit medications to be released at the right time, and electronic diaries, contributed to fostering adherence by leveraging advancements in digital health (Farach et al. 2012; Choi 2015; Kamusheva et al. 2020; Rüther et al. 2021; Orso et al. 2022). Behavioral interventions such as motivational interviewing with specialists from multidisciplinary teams seem effective in improving MA (Malik et al. 2015; Alexander et al. 2017; Vaisbich et al. 2019; González-Lamuño et al. 2021). Other MAEIs addressed patient preferences about the type of therapy, administration frequency, treatment duration, and reduction in patient cost burden (De Moerloose et al. 2008; Cappellini and Taher 2009; Thomson et al. 2011; Pogna et al. 2021; Acquadro et al. 2022; Orso et al. 2022). The different MAEIs are summarized in Fig. 4.

## Consequences of nonadherence to therapy

Non-adherence to therapy results in poor patient outcomes, increasing healthcare service utilization and overall costs. In our study, MNA was one of the factors contributing to frequent hospital readmissions or prolonged stays (Shenoy et al. 2015; Chaudhary et al. 2017; Ueda et al. 2019; Vitturi et al. 2020; Dong et al. 2022). The condition and quality of life of non-compliant with the treatment patients could worsen, and new previously unexperienced symptoms may appear (Gallin et al. 2003; Chaudhary et al. 2017; Westermann et al. 2019; Vitturi et al. 2020; Dong et al. 2022). Strict adherence to therapy can result in complete remission of RD or its complications, opposing previous claims (Westermann et al. 2019). MNA led to greater resource utilization and costs (Jabbour et al. 2012; Chen 2016; Lashilola et al. 2023). A recent study shows that improving MA in patients with kidney failure would result in savings of approximately £25,000 per patient in the UK (Lashilola et al. 2023).

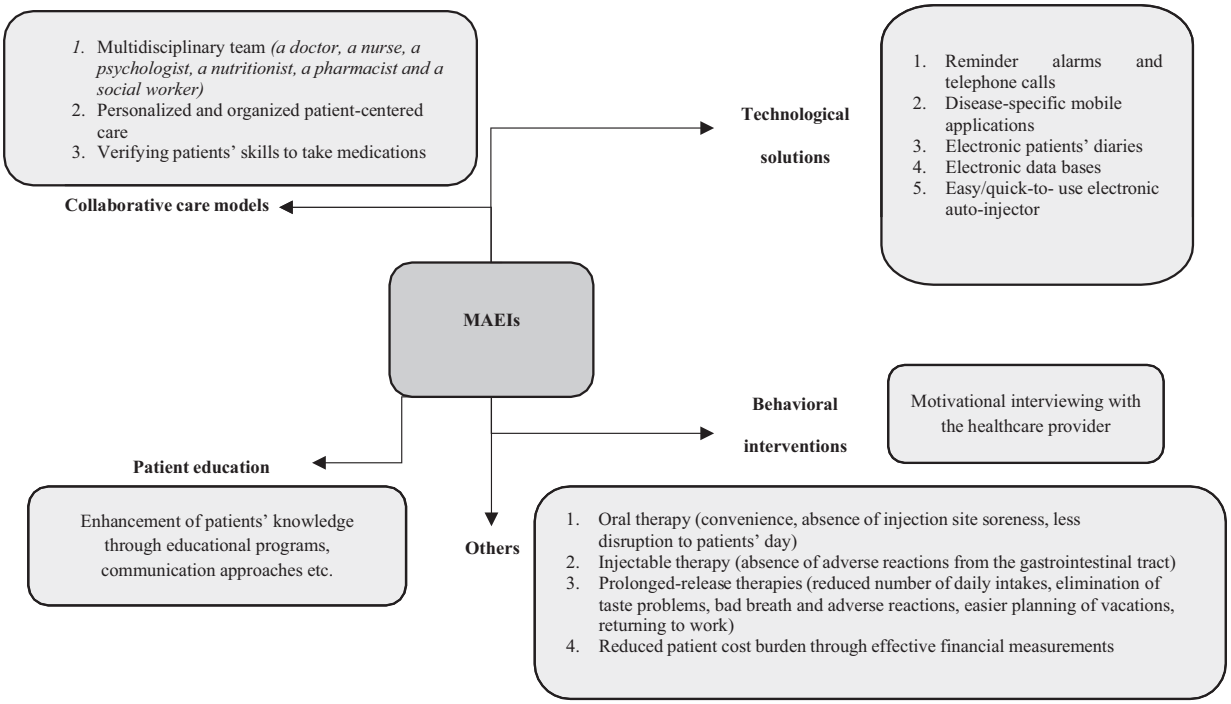


**Figure 4.** Factors for enhancing medication adherence among patients with rare diseases.

# Discussion

## Statement of key findings

The study highlights several critical aspects related to MA among patients with RDs, including the level of MA, assessment methods, and improvement strategies. The number of published studies inciting MA among patients with RDs increased in recent years. Notably, adherence levels showed significant variability, ranging from 0% (complete rejection of therapy) to 97.7% (excellent MA). Despite the importance of MA topics, there are no standardized methods for measuring and reporting MA among patients with RDs, which represents a significant gap in clinical practice. Logically, we revealed that the level of MA is influenced by the same factors identified in other patient populations, as well as by the consequences of MNA. The findings suggest that improving MA would enhance patient outcomes and reduce the economic burden of RDs by reducing hospitalizations and optimizing treatment efficacy.

In our study, the primary reasons for non-adherence were therapy-related and patient-related factors. The most commonly cited reasons in the first group were side effects (Cappellini and Taher 2009; Costa et al. 2012; Ivarsson et al. 2018; Vatier et al. 2019; Kamusheva et al. 2020; Pogna et al. 2021; Acquadro et al. 2022; Orso et al. 2022; Hollmen et al. 2023) and the need for multiple drug administrations daily or weekly (Cappellini and Taher 2009; Thomson et al. 2011; Vitturi et al. 2020; Torregrosa Prats et al. 2021; Hollmen et al. 2023). On the other hand, adolescence was one of the most cited patient-related reasons for MNA (De Moerloose et al. 2008; Jabbour et al. 2012; Malik et al. 2015; Medina and Román 2020; González-Lamuño et al. 2021), which is probably due to denial of the severity of the disease, concerns about side effects such as weight gain or other changes in appearance, the convenience of not taking the drug, fear of their friends seeing medication intake, and psychological aspects such as stress, anxiety, depression, and others (Taddeo et al. 2008; Anon 2016). Other reasons for MNA related to the patients were forgetfulness and low education level. The findings in this review underline again the need to improve the educational programs for patients, which can be pointed toward the whole family or the individual.

The consequences of MNA affect not only the individual but also the whole society and health system. For instance, MNA among patients with RD could lead to exacerbation of the patient's condition, resulting in disability and/or death (Gallin et al. 2003; Jabbour et al. 2012; Shenoy et al. 2015; Chen 2016; Chaudhary et al. 2017; Ueda et al. 2019; Westermann et al. 2019; Vitturi et al. 2020; Dong et al. 2022; Lashilola et al. 2023). Considering the complexity of RD, it is unsurprising that patients with RD are more likely to visit a hospital (46.1%) than patients without RD (23.6%, $p < 0.0001$) (Bennett et al. 2019). In addition, numerous studies have concluded that non-adherence to therapy for chronic diseases is a major cause of frequent and/or longer hospital admissions (Iuga and McGuire 2013; Payero et al. 2014; Mongkhon et al. 2018). The societal and economic burdens associated with MNA are substantial, manifesting as increased direct and indirect costs (Jabbour et al. 2012; Chen 2016; Lashilola et al. 2023). These costs are projected to continue increasing, as concluded by a study from 2018, which also reported that the annual costs of MNA range from $949 to $44,190 per person (Cutler et al. 2018).

The clinical guideline "Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence" (2009) focuses on patient-centered care. It explains the necessity for making informed decisions about therapy and active involvement in the treatment process. According to this guideline, no universal MAEI exists (NICE 2009). Health systems could implement diverse and effective strategies to identify nonadherent patients and the underlying reasons for MNA. However, due to the wide variety of RDs, it is important to individualize and select the most suitable approach for each patient. A multidisciplinary team is required to provide comprehensive care and information, answer questions that arise, and follow up with patients during therapy. This care includes timely addressing of adverse events and ensuring treatment adherence. One of the most important things when living with a lifelong condition is for the patient to not feel alone during the journey and to believe that the prescribed therapy is effective for their condition. For this reason, establishing a robust social support system to aid patients in MA can have a profound impact on MA levels (Malik et al. 2015; Walburn et al. 2019; Wang et al. 2022; Nguyen et al. 2023). Considering MAEIs included in our study, both patients and healthcare professionals believe mobile apps can significantly enhance adherence rates. While numerous apps are currently available that target common chronic diseases, very few apps address RDs. For instance, an application was developed to assist patients with rare inborn errors of metabolism in adhering to a strict diet that was essential for controlling the disease (Ho et al. 2016). Additionally, companies have created digital apps to support patients throughout the diagnosis, acceptance, and treatment phases (Atlantis Health 2023). These innovative solutions hold promise for improving adherence and enhancing the overall management of RDs.

## Strengths and weaknesses

To the best of our knowledge, this is one of the few comprehensive, systematic, and rigorous reviews that analyze MA issues related to patients with RDs. In line with our methodology, we reassessed the 20 articles from our prior search to ensure a consistent and thorough evaluation

of all relevant data. Re-including these studies ensures that we capture all relevant data, enhancing the robustness of our findings and ensuring a more comprehensive review. It attempts to target all types of studies and RDs covered in the scientific literature. Thus, considering all specifics and nationally-based practices, a broad "picture" of the current situation regarding MA issues in this group of patients could be drawn and analyzed. The current study could be used as a basis for developing further policies and good practices for improving MA management, thus avoiding the negative consequences of nonadherence.

However, it is essential to acknowledge certain limitations of the study. First, the search was limited to studies published in English, potentially excluding valuable contributions in other languages. Additionally, the diversity in methodologies, designs, data collection methods, sample sizes, and evaluation criteria across the included publications posed challenges for direct comparisons and meta-analyses. The literature reviews (n = 6) included in our study were not assessed with the JBI tool or MMAT, as they failed to meet the criteria for evaluation. Another limitation is that this SR was restricted to articles published solely in the PubMed electronic database, unlike our previous scoping review, which covered two databases: PubMed and Google Scholar. This narrow focus may have inadvertently overlooked relevant studies in other databases or sources.

### Interpretation of findings

This review can be useful in future efforts to improve patient and public reporting systems for MA. Currently, there is an absence of developed and implemented methods for measuring, reporting, and improving MA in patients with RD. This reduces the potential for achieving optimal therapeutic outcomes. Therefore, care management programs are needed to understand the underlying causes of MNA. Such insights are critical for the development and implementation of innovative and effective solutions. A targeted approach is needed, combining different measures and focusing on overcoming the barriers that influence MA. Only when HCPs better and fully understand the reasons leading to MNA can they provide targeted assistance and effective interventions (Atlantis Health, 2023). It is also crucial to develop guidelines that indicate when and how information about the treatment should be given without causing concern to the patients. Given that frequent hospital admissions are the most common consequence of MNA, the implementation of government-supported home therapy programs is paramount. Problems with access to medicines (i.e., financial ones, lack of therapy on the market, etc.) must be eradicated as a prerequisite for MNA. Additionally, disparities in drug reimbursement policies across different countries contribute to unequal access to treatment, affecting patients' ability to adhere to prescribed regimens (Pejcic et al. 2018).

### Further research

Further research is crucial to fully understand how patient characteristics, such as age, gender, education, residence, and occupation, impact therapy adherence. Additionally, more research is needed to evaluate the preferences of patients with RDs regarding the use of various MAEIs. It is also important to examine how different methods to increase therapy adherence affect the overall adherence percentage. Research should also aim to develop standardized methods for measuring and reporting MA, as well as strategies that can be integrated into healthcare systems to identify non-adherent patients early and provide targeted support.

## Conclusion

Significant variability in MA exists among patients with RDs, depending on the assessment method and the specific disease. Still, no dedicated approach within the national legal framework is being developed to address MNA issues in these patients. Therefore, it is essential to develop national programs and guidelines specifically tailored to RDs. These guidelines should establish clear protocols for measuring, improving, and managing MA. By implementing comprehensive frameworks and interventions, healthcare systems and society can significantly enhance support for patients with RDs in adhering to their medication regimens and ultimately improving their health outcomes.

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## Additional information

### Conflict of interest

The authors have declared that no competing interests exist.

### Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

## Author contributions

An initial idea for this review was given by MK. IH and PP conducted the literature search and data analysis. The initial draft of the manuscript was written by IH and was critically revised by MK. All authors have carefully reviewed and given their approval to the final version of the manuscript. The authors have reached a consensus on which journal they will submit the article to.


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## Data availability

All of the data that support the findings of this study are available in the main text or Supplementary Information.

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## Supplementary material 1

### PRISMA 2020 checklist

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## Supplementary material 2

### Database search strategy in PubMed database

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## Supplementary material 3

### Risk of bias assessment (MMAT tool)

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## Supplementary material 4

### Critical appraisal of included systematic reviews with JBI tool

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## Supplementary material 5

### Characteristics of included studies

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