Expert Review of Clinical Immunology

ISSN: 1744-666X (Print) 1744-8409 (Online) Journal homepage: http://www.tandfonline.com/loi/ierm20

Medication adherence in patients with rheumatoid arthritis: a critical appraisal of the existing literature

Bart JF van den Bemt, Hanneke E Zwikker & Cornelia HM van den Ende

To cite this article: Bart JF van den Bemt, Hanneke E Zwikker & Cornelia HM van den Ende (2012) Medication adherence in patients with rheumatoid arthritis: a critical appraisal of the existing literature, Expert Review of Clinical Immunology, 8:4, 337-351, DOI: 10.1586/eci.12.23

To link to this article: http://dx.doi.org/10.1586/eci.12.23

Published online: 10 Jan 2014.

EXPERT REVIEWS

Medication adherence in patients with rheumatoid arthritis: a critical appraisal of the existing literature

Expert Rev. Clin. Immunol. 8(4), 337–351 (2012)

Bart JF van den Bemt*[1], Hanneke E Zwikker[2] and Cornelia HM van den Ende[2]

[1]*Department of Pharmacy, Sint Maartenskliniek, PO Box 9011, 6500 GM, Nijmegen, The Netherlands*
[2]*Department of Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands*
**Author for correspondence:*
Tel.: +31 24 365 9061
Fax: +31 24 365 9827
b.vandenbemt@maartenskliniek.nl

Adherence to medication in patients with rheumatoid arthritis is low, varying from 30 to 80%. Improving adherence to therapy could therefore dramatically improve the efficacy of drug therapy. Although indicators for suboptimal adherence can be useful to identify nonadherent patients, and could function as targets for adherence-improving interventions, no indicators are yet found to be consistently and strongly related to nonadherence. Despite this, nonadherence behavior could conceptually be categorized into two subtypes: unintentional (due to forgetfulness, regimen complexity or physical problems) and intentional (based on the patient's decision to take no/less medication). In case of intentional nonadherence, patients seem to make a benefit–risk analysis weighing the perceived risks of the treatment against the perceived benefits. This weighing process may be influenced by the patient's beliefs about medication, the patient's self-efficacy and the patient's knowledge of the disease. This implicates that besides tackling practical barriers, clinicians should be sensitive to patient's personal beliefs that may impact medication adherence.

Keywords: adherence • beliefs about medication • compliance • DMARDs

Financial & competing interests disclosure
EDITOR
Elisa Manzotti, *Publisher, Future Science Group, London, UK*
Disclosure: *Elisa Manzotti has disclosed no relevant financial relationships.*
CME AUTHOR
Charles P Vega, MD, *Health Sciences Clinical Professor; Residency Director, Department of Family Medicine, University of California, Irvine, CA, USA*
Disclosure: *Charles P Vega, MD, has disclosed no relevant financial relationships.*
AUTHORS
Bart JF van den Bemt, PharmD, PhD, *Department of Pharmacy, Sint Maartenskliniek, Nijmegen, The Netherlands*
Disclosure: *Bart JF van den Bemt, PharmD, PhD, has disclosed no relevant financial relationships.*
Hanneke E Zwikker, MSc, *Department of Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands*
Disclosure: *Hanneke E Zwikker, MSc, has disclosed no relevant financial relationships.*
Cornelia HM van den Ende, PhD, *Department of Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands*
Disclosure: *Cornelia HM van den Ende, PhD, has disclosed no relevant financial relationships.*

The prescription of a medicine is one of the most common interventions in the healthcare system. However, the full benefit of pharmacological interventions can only be achieved if patients follow drug regimens closely. Adherence is, however, low in chronic medical conditions: approximately 50% of all people with chronic medical conditions do not adhere to their prescribed medication regimens [1,2]. The implications of nonadherence are far reaching, as nonadherence may severely compromise the effectiveness of treatment and increase healthcare costs; for example, the cost of nonadherence in the USA has been estimated to reach US$100 billion annually [3]. The reduction of nonadherence is therefore thought likely to have a greater effect in health than further improvements in traditional biomedical treatment [4].

Medication nonadherence has negative consequences on the pharmacological treatment of rheumatoid arthritis (RA), as disease-modifying antirheumatic drugs (DMARDs) reduce disease activity and radiological progression and improve long-term functional outcome in patients with RA [5]. Nonadherence is associated with disease flares and increased disability, for example [6,7]. Despite this, adherence rates to prescribed medicine regimes in people with RA are low, varying from 30 to 80% [7–22]. Improving adherence to therapy could therefore dramatically improve the efficacy of medical treatments and reduce costs associated with RA.

The purpose of this critical narrative appraisal of the literature is to give a broad overview of the existing literature on medication nonadherence and adherence to disease-modifying drugs in RA, by addressing adherence terminology, measuring nonadherence, the extent of the problem and risk factors for nonadherence, and by providing a short overview of interventions to improve medication adherence among people with RA. Available studies published until July 2011 on medication adherence in RA were searched for using an electronic literature search in PubMed. The search strategy is described in TABLE 1.

Table 1. Search strategy in PubMed for retrieving studies on medication adherence in rheumatoid arthritis.

Boolean operator	Text words and Medical Index Subject Headings
	Arthritis, rheumatoid [mesh terms] or rheumatoid arthritis[tw]
AND	Medication adherence [mesh terms] or patient compliance [mesh terms]-or-(medication[tw] or medicine[tw] or medicines[tw] or medical[tw] or therapy[tw] or therapie[tw] or drug[tw] or drugs[tw]) and (complian* or non-complian* or non complian* or noncomplian* or adher* or non-adher* or non adher* or nonadher* or persist* or non-persist* or non persist* or nonpersist*)
AND	adult[mesh terms] or mature [tw] or adult [tw]

Adherence terminology: adherence, compliance & concordance

The terminology used in the area of medicine-taking reflects the changing understanding of medicine-taking behavior and the changing relationships between healthcare professionals and patients. In the medical literature of the 1950s, the term 'compliance' was used. This term, strongly led by a physician-based approach, was defined as the extent to which patient's behavior coincides with medical advice [23]. However, the word compliance became quickly unpopular for its judgmental overtones. Therefore, the term 'adherence' was introduced as an alternative to compliance. It comes closer to describing and emphasizing patient and clinician collaboration in decisions, rather than conveying the idea of obedience to a medical prescription [24–26]. 'Medication adherence' can be defined as the extent to which a patient's behavior, with respect to taking medication, corresponds with agreed recommendations from a healthcare provider [101].

Medication adherence can be divided into three major components: persistence (defined as the length of time a patient fills his/her prescriptions); initiation adherence (does the patient start with the indented pharmacotherapy); and execution adherence (the comparison between the prescribed drug dosing regimen and the real patient's drug-taking behavior). Execution adherence includes dose omissions (missed doses) and the so-called 'drug holidays' (3 or more days without drug intake).

In the mid 1990s, the concept of 'concordance' was born. The term 'concordance' relates to a process of the consultation in which prescribing is based on partnership. In this process, healthcare professionals recognize the primacy of the patient's decision about taking the recommended medication, and the patient's expertise and beliefs are fully valued. The term 'concordance' overtly recognizes that for optimal medication use, the patient's

opinion on medication should be taken into account and discussed throughout the therapy. This discussion will help to foster a patient–physician relationship in which the patient is able to communicate as a partner in the selection of treatment and the subsequent review of its effect. Therefore, compliance focuses on the behavior of one person (the patient), whereas concordance requires the participation of at least two people.

Measuring nonadherence

The validity of adherence assessment is based on the method of measurement. The minimum requirements of a gold standard for adherence measurement include:

- Validity: proving ingestion of the medication and giving a detailed overview about timing and ingestion;
- Reliability and sensitivity to change: stable results under stable adherence and differential results under variable adherence;
- Feasibility: the patient should not be aware of adherence measurement and should not be able to censor the result.

Although it is ethically desirable that patients know that his/her medication use is being followed, the consciousness of being monitored may increase a patient's adherence. Moreover, the assessment should be easy to use and the method should be noninvasive. Unfortunately, a single instrument fulfilling these properties is currently unavailable [27]. Despite the absence of a gold standard, adherence can be measured in a variety of ways, as depicted in Table 2 [9,10,28,29].

Subjective measurement

The simplest assessment of medication adherence is frequently used, and involves asking the patient whether he or she is taking the medications as prescribed. Although patient self-report may be 100% specific for being nonadherent, this method is relatively insensitive for the detection of nonadherence (which is confirmed in several studies showing that the answers of the patient are not always accurate). In fact, patients claiming to be adherent may under-report their nonadherence to avoid caregiver disapproval [30]. Furthermore, self-report is time-dependent, since patients have the best recall for adherence in the last 24-h period.

Studies have consistently shown that third-party assessments (e.g., assessment by healthcare providers) are unreliable and tend to overestimate patient adherence [30]. Physician's estimate of patient's adherence correlated poorly with objective pill counts [31]. In more detail, physicians seem to detect good adherence well (specificity ~90%), but were not good at predicting poor or partial adherence [32].

Direct objective measurement

Direct methods prove directly that the medication has been taken by the patient. Examples of direct methods include direct observation and measurement of serum drug/metabolite levels or biological markers. Although no method is 100% reliable, direct measurements have low bias, although these methods may be expensive and inconvenient for patients.

Furthermore, the use of biological markers only reflects short-term adherence, and can overestimate patients' long-term adherence due to the tooth-brush effect/white coat adherence. This phenomenon takes its name from the fact that dentists often see patients beginning to brush their teeth only a few days before the appointment. This can also be the case for drug taking, implicating that only drug/metabolites with long elimination half-lives are fair predictors for nonadherence. Interindividual differences in drug absorption and metabolism can also lead to inaccurate conclusions regarding medication adherence.

Table 2. Methods to assess adherence.

Method of assessment	Advantage	Disadvantage
Subjective		
Self-report	Easy to use Readily available Noninvasive Sensitive for nonadherence Inexpensive	No evidence that the drug is actually ingested Not accurate Patient is aware of the measurement
Physicians' estimation	Easy to use Inexpensive Noninvasive	Not accurate
Direct		
Biomarkers (drug concentration/metabolites)	Objectively proves ingestion of the medication Accurate	Sensitive for white coat adherence Invasive Expensive Varies with individual difference in metabolism
Indirect		
Pharmacy refill	Inexpensive Noninvasive Patient is not aware that they are being monitored	No evidence that the drug is actually ingested once filled
Tablet counts	Easy to use Inexpensive Noninvasive	No evidence that the drug is actually ingested once filled
Electronic monitors	Noninvasive Objective Provides additional information about dosing interval	Patient is aware of the measurement
Questionnaires	Easy to use Noninvasive Validation possible	Patient is aware of the measurement

Indirect measurement

Indirect methods are the most common approach to measuring medication adherence. Commonly used indirect measures include: pharmacy refills; electronic monitoring; tablet counts; and questionnaires.

Pharmacy refills

Pharmacy refills provide a convenient, noninvasive, objective and inexpensive method for estimating medication adherence and persistence. Calculation of a patient's refill adherence is especially suited for large populations of (chronic) medication users. However, the extent of adherence obtained from pharmacy refill data does not provide the patient's medication consumption information, but rather provides the acquisition of the medication. Pharmacy refill data are therefore especially specific for identifying nonadherent patients [33]. However, a number of different measures and definitions of adherence and persistence have been reported in the published literature. The appropriateness and choice of the specific measure employed should be determined by the overall goals of the study, as well as the relative advantages and limitations of the measures. A commonly used method is the medication possession ratio, often defined as the proportion of days supply obtained during a specified time period or over a period of refill intervals. However, it is important to notice that various methods of calculation of the medication possession ratio exist. Therefore, it is important to evaluate how the medication possession ratio was calculated when interpreting literature regarding patient adherence [34].

Electronic monitoring devices

Electronic monitoring devices, such as the Medication Event Monitoring System (MEMS) can be used to provide accurate and detailed information on medication-taking behavior [35,36]. These devices compile the dosing histories of patients' prescribed medication, registering the number of pills missed, as well as deviations from the dosing schedule. The availability and costs of MEMS devices could limit the feasibility of its use [28,37,38]. Another disadvantage of electronic monitoring devices is the fact that an electronic device may increase the patient's awareness about the fact that his/her adherence will be monitored. Although the boxes can be opened without medication being taken, MEMS devices have been shown to have superior sensitivity compared with other methods for the assessment of medication adherence.

Tablet counts

Tablet counts are frequently used in clinical trials and adherence research, but are notoriously unreliable and usually provide overestimates [17,27]. Although using tablet counts offers advantages such as low costs, and relatively simple data collection and calculation, the accuracy of the assessment relies on the patient's willingness to return unused medication [39]. As a consequence, adherence may be overestimated, as patients can manipulate the tablet count by dumping the medication prior to the scheduled visits, leading to an overestimation of adherence. Furthermore, the reliability of the pill count is also dependent on the correct number of drugs being dispensed and counted.

Questionnaires

Although a number of self-report medication adherence questionnaires have been described in the literature, no gold standard questionnaire for the assessment of nonadherence and adherence in RA exists. Three adherence questionnaires are most widely used in RA: the Morisky questionnaire [40]; the Medication Adherence Report Scale (MARS) [41]; and the Compliance Questionnaire on Rheumatology [42,43]. The Morisky scale is a commonly used questionnaire that consists of four questions on reasons for nonadherence, which are answered with a yes/no response. The measure has been found to have adequate internal consistency (Cronbach's $\alpha = 0.61$), a good sensitivity (0.81) and moderate specificity (0.44) when validated to non-RA clinical parameters such as blood pressure [40,44]. The Morinsky scale is not yet validated in RA. The MARS has been used in a variety of patients (e.g., patients with asthma, chronic obstructive pulmonary disease, high cholesterol, RA and diabetes) [41]. Four of the five items in the MARS are related to intentional nonadherence, such as the tendency to avoid, forget, adjust and stop taking medication, whereas one MARS item focuses on forgetting medication [16,45]. However, both the Morisky scale and the MARS did not perform well compared with an electronic MEMS in transplant recipients taking oral steroids and immunosuppressants [45].

Currently, there is only one rheumatology-specific adherence measure: the 19-item Compliance Questionnaire on Rheumatology. This questionnaire has been validated in patients with inflammatory rheumatic diseases against a MEMS device [13]. The 19-item Compliance Questionnaire on Rheumatology compares well with electronic monitoring over 6 months, with a sensitivity of 0.98, a specificity of 0.67 and an estimated κ of 0.78 to detect nonadherence [13,42,43].

In conclusion, although a wide variety of methods have been used to assess nonadherence and adherence, a gold standard for adherence assessment is lacking. Although objective methods (e.g., blood or urine samples, pharmacy refill data, electronic pill monitoring or pill counts) are considered to be more reliable than subjective methods, they are in general more expensive and more complicated than subjective methods. Urine and serum samples are constrained by interindividual variations, whereas pill counts and electronic devices assume that patients really take their medication when they pick up the drug in the pharmacy and/or open the bottle of pills. Although subjective measures are cheap and relatively easy to use, the psychometric properties of these instruments are often poor; patient self-reported adherence is often poorly associated with adherence rates assessed with a MEMS device and pill count [46–49]. It has been suggested that adherence may be underestimated by MEMS and overestimated by patient self-report and pill count [49].

Extent of the problem: adherence to traditional & biological DMARDs

Studies reporting adherence rates on both traditional and biological DMARDs are listed in Table 3. Despite the varied extent of nonadherence found in these studies, they all confirm that adherence in RA is still suboptimal. Nine studies exclusively

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.