

Patients' Attitudes and Experiences of Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis and Spondyloarthritis: A Qualitative Synthesis

AYANO KELLY,¹ KATHLEEN TYMMS,² DAVID J. TUNNICLIFFE,³ DANIEL SUMPTON,⁴ CHANDIMA PERERA,⁵ KIERAN FALLON,⁶ JONATHAN C. CRAIG,³ WALTER ABHAYARATNA,⁶ AND ALLISON TONG³

Objective. Nonadherence to disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) and spondyloarthritis (SpA) results in increased disease activity and symptoms and poorer quality of life. We aimed to describe patients' attitudes and experiences of DMARDs in RA and SpA to inform strategies to improve medication adherence.

Methods. Databases (MEDLINE, Embase, PsycINFO, and CINAHL) were searched to January 2016. Thematic synthesis was used to analyze the findings.

Results. From 56 studies involving 1,383 adult patients (RA [n = 1,149], SpA [n = 191], not specified [n = 43]), we identified 6 themes (with subthemes): intensifying disease identity (severity of sudden pharmacotherapy, signifying deteriorating health, daunting lifelong therapy), distressing uncertainties and consequences (poisoning the body, doubting efficacy, conflicting and confusing advice, prognostic uncertainty with changing treatment regimens), powerful social influences (swayed by others' experiences, partnering with physicians, maintaining roles, confidence in comprehensive and ongoing care, valuing peer support), privilege and right of access to biologic agents (expensive medications must be better, right to receive a biologic agent, fearing dispossession), maintaining control (complete ownership of decision, taking extreme risks, minimizing lifestyle intrusion), and negotiating treatment expectations (miraculous recovery, mediocre benefit, reaching the end of the line).

Conclusion. Patients perceive DMARDs as strong medications with alarming side effects that intensify their disease identity. Trust and confidence in medical care, positive experiences with DMARDs among other patients, and an expectation that medications will help maintain participation in life can motivate patients to use DMARDs. Creating a supportive environment for patients to voice their concerns may improve treatment satisfaction, adherence, and health outcomes.

INTRODUCTION

Patients with rheumatoid arthritis and spondyloarthritis (including ankylosing spondylitis, psoriatic arthritis, and arthritis associated with inflammatory bowel disease) can experience progressive joint damage, deformity, and disability, which can limit functioning and impair quality of life

(1–4). Disease-modifying antirheumatic drugs (DMARDs) are recommended first-line treatment, using a treat-to-target strategy, particularly for rheumatoid arthritis and psoriatic arthritis, with the aim of decreasing joint inflammation, achieving remission, and preventing permanent damage (5,6). Yet nonadherence to DMARDs remains a major clinical challenge.

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¹Ayano Kelly, MBBS, FRACP: Canberra Rheumatology and Australian National University, Canberra, Canberra Hospital, Woden, Australian Capital Territory, and The Children's Hospital at Westmead, Westmead, New South Wales, Australia; ²Kathleen Tymms, MBBS, FRACP: Canberra Rheumatology and Australian National University, Canberra, and Canberra Hospital, Woden, Australian Capital Territory, Australia; ³David J. Tunnicliffe, MPH, Jonathan C. Craig, PhD, Allison Tong, PhD: The Children's Hospital at Westmead, Westmead, and Sydney School of

Public Health, The University of Sydney, Sydney, New South Wales, Australia; ⁴Daniel Sumpton, MBBS, FRACP: The Children's Hospital at Westmead, Westmead, and Liverpool Hospital and Ingham Institute for Applied Medical Research, Liverpool, New South Wales, Australia; ⁵Chandima Perera, MBBS, FRACP: Canberra Hospital, Woden, Australian Capital Territory, Australia; ⁶Kieran Fallon, MD, Walter Abhayaratna, PhD: Canberra Hospital, Woden, and Australian National University, Canberra, Australian Capital Territory, Australia.

Address correspondence to Ayano Kelly, MBBS, FRACP, Canberra Rheumatology, 9th Floor Canberra House, 40 Marcus Clarke Street, Canberra City, Australia 2601. E-mail: Ayano.Kelly@anu.edu.au.

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Significance & Innovations

- Patients with rheumatoid arthritis/spondyloarthritis equate disease-modifying antirheumatic drugs with intensifying disease identity and distressing uncertainties and consequences.
- Negotiating treatment expectations with a trustworthy, confident, and knowledgeable physician may improve medication adherence.
- Patients wish to maintain control, are swayed by social influences, and appreciate privileged biologic agent access.

Research estimates that only 66% of patients with rheumatoid arthritis are adherent to DMARDs (7). Nonadherence is associated with disease flares, increased disability, and health care costs in rheumatoid arthritis (8,9). The patient-physician relationship, patients' beliefs about medications, knowledge about their disease, and self-efficacy have been consistently identified as modifiable factors associated with adherence in rheumatoid arthritis (7,10–12). However, studies have not consistently demonstrated that patient and treatment characteristics, including age, sex, disease duration, number of medications, and side effects, are associated with adherence (12,13).

International rheumatology guidelines emphasize shared decision making in rheumatoid arthritis and spondyloarthritis (5,6,14). Shared decision making requires a comprehensive and detailed understanding of the patients' values, priorities, and preferences, yet there is sparse

qualitative evidence for this approach in relation to DMARDs. A thematic synthesis of multiple qualitative studies can summarize and extend qualitative research in a defined field (15). A systematic review of qualitative studies has been performed in lay experiences of medicine taking across multiple conditions (16). This study aims to describe patients' attitudes and experiences of DMARDs in rheumatoid arthritis and spondyloarthritis. The findings may be used to develop strategies, models, and interventions to improve treatment adherence, satisfaction, and health-related outcomes.

MATERIALS AND METHODS

We followed the Enhancing Transparency of Reporting the Synthesis of Qualitative Research framework (17). The systematic review does not require ethics approval by an institutional review board or ethical review board in accordance with the policy of the authors' institutions.

Selection criteria. Qualitative studies that reported the perspectives and experiences of adults (ages ≥ 18 years) with rheumatoid arthritis or spondyloarthritis taking DMARDs were eligible. Observational epidemiologic studies, nonprimary research articles (letters, commentaries, and reviews), and non-English articles were excluded.

Data sources and searches. We searched MEDLINE, Embase, CINAHL, and PsycINFO from database inception to January 12, 2016 (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at <http://online.library.wiley.com/doi/10.1002/acr.23329/abstract>). We also hand searched reference lists of relevant studies and

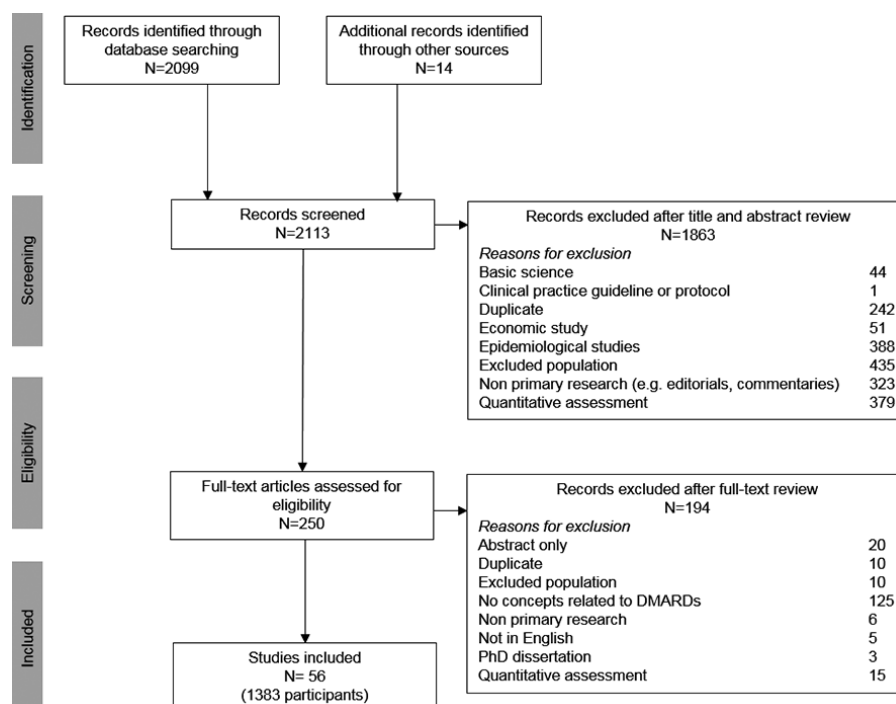


Figure 1. Search results. DMARDs = disease-modifying antirheumatic drugs.

searched Google Scholar for additional studies. We screened the abstracts and examined the full text of potentially relevant studies.

Comprehensiveness of reporting. We used a modified version of the Consolidated Criteria for Reporting Qualitative Health Research framework (COREQ) (18) to evaluate the completeness of reporting of each interview study. Items specific to the research team, methods, setting, analysis, and interpretations were assessed. Three reviewers (AK, DJT, DS) independently assessed each study and resolved disagreements through a fourth reviewer (AT).

Synthesis of findings. We used thematic synthesis for data analysis. We extracted all participant quotations and text under the results and/or discussion/conclusion sections and imported them into HyperResearch 2015 software, version 3.7.3. One author (AK) inductively identified preliminary concepts. The preliminary coding framework was discussed among authors (AK/KT/DJT/DS/AT) to ensure the codes reflected the full range and depth of data. For each article, AK performed line-by-line coding into themes and sub-themes and refined them iteratively. Other authors (AK/DJT/AT) identified conceptual links among themes to develop an analytical thematic schema.

RESULTS

Literature search and study descriptions. From 2,113 citations, we included 56 studies involving 1,383 participants (Figure 1). Study characteristics are provided (Table 1 and Supplementary Table 2, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23329/abstract>). Participants were ages 26–86 years, 851 women (62%), 423 men (31%), and 109 sex unspecified (8%). A total of 1,149 participants had rheumatoid arthritis (83%), and 191 had spondyloarthritis (14%). The type of arthritis was unspecified in 43 participants (3%). Disease duration was <1 month to 49 years. Eighteen studies had participants taking biologic DMARDs (32%), 3 studies had conventional DMARDs (5%), 8 studies had both DMARD groups (14%), and type of medication was unspecified in 27 studies (48%).

Comprehensiveness of reporting. The comprehensiveness of reporting was variable, with interview studies ($n = 51$) reporting 5–21 of the 26 items in the modified COREQ framework (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23329/abstract>). Twenty-four studies (47%) documented data saturation, and 44 studies (86%) specified the use of researcher triangulation. Participant quotations were provided in 49 studies (96%).

Synthesis. We identified 6 themes: intensifying disease identity, distressing uncertainties and consequences, powerful social influences, privilege and right of access to biologic agents, maintaining control, and negotiating treatment expectations. The subthemes are described in the following sections, with illustrative quotations in Supplementary

Table 1. Characteristics of included studies ($n = 56$)*

Study characteristics	No. (%)
Year of publication	
1990–2010	28 (50)
2011–2016	28 (50)
Region†	
UK	27 (48)
US	5 (9)
Canada	5 (9)
Australia	2 (4)
Europe	16 (29)
Other‡	2 (4)
Sample size	
1–20	29 (52)
21–40	21 (38)
41–60	1 (2)
61–80	0 (0)
>80	3 (5)
Not reported	2 (4)
Type of arthritis	
RA	41 (73)
RA and spondyloarthritis	7 (13)
Spondyloarthritis	4 (7)
Not reported	4 (7)
Type of DMARD	
Biologic DMARD	18 (32)
Conventional and biologic DMARD	8 (14)
Conventional DMARD	3 (5)
Not reported	27 (48)
Method of data collection	
Interviews	33 (59)
Focus groups	10 (18)
Interviews and focus groups	8 (14)
Other	5 (9)

* RA = rheumatoid arthritis; DMARD = disease-modifying anti-rheumatic drug.

† One study was conducted in multiple countries.

‡ Ireland, Turkey (1 study each).

Table 4 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23329/abstract>). The conceptual links among themes are shown in Figure 2.

Intensifying disease identity. “The more medication you take...the more ill you feel. Maybe even more than you really are” (19). This theme describes how DMARDs intensified the patients’ feelings of being unwell, which occurred throughout the patient’s journey from diagnosis, during DMARD escalation and chronic maintenance therapy.

Severity of sudden pharmacotherapy. After being diagnosed with arthritis, some patients were shocked with having to take medications for the first time and by how strong the medications were. Patients who avoided medications previously could be particularly alarmed and view DMARDs to be both unexpected and unwarranted. Some chose not to start their medications because it would mean they were seriously ill (19), or they were frightened by the side effects of their first medication: “If this is the drug they start with (methotrexate), what will be the side effects of the next drug?” (19).



Figure 2. Thematic schema. Patients equate medications with being ill and are terrified of side effects, uncertain of treatment efficacy, and confused when receiving insufficient or conflicting medical advice. A trustworthy doctor, supportive health environment, and positive family influences and experiences of others can mitigate patient fears and improve their medication experience. Patients desire to maintain control of their disease, their social roles, and their decision to take medications sometimes at extreme costs. Some patients are pleasantly surprised by their treatment outcomes, while others are repeatedly disappointed. DMARDs = disease-modifying antirheumatic drugs.

Signifying deteriorating health. Being placed on increasing numbers of medications was a sign of worsening illness and created concerns about potential drug interactions. Therefore, reducing medications could be an indicator of improving health and a primary health goal. When patients forgot to take their medications because they felt well, they interpreted forgetting their medications as a sign of good health.

Daunting lifelong therapy. Patients despaired being required to take lifelong medications, a reminder that their arthritis was incurable. When some patients stopped their medications, symptoms returned and their ability to function decreased. This relapse made patients feel physically dependent on medications and provoked anxiety about long-term side effects.

Distressing uncertainties and consequences. “My orthopedist said ‘arthritis patients actually have 2 diseases, that is arthritis and methotrexate.’ I have always remembered that” (20). This theme describes the difficulty and fear patients experience due to uncertainty in relation to DMARD safety and efficacy. Fears can be further heightened during times of DMARD changes and from comments by other health professionals.

Poisoning the body. DMARDs were perceived to be strong, toxic (21) medications that could damage internal organs, increase mortality, and increase the risk of having cancer because of immune suppression. Patients were aware that methotrexate is used to treat cancer, which made them feel they were taking a “very, very strong drug” (22) equivalent to chemotherapy. Patients expressed concern about both conventional and biologic DMARDs. Some reluctantly accepted the medication because of necessity:

“Hate it, but can’t do without it” (23). Others preferred taking alternative medications that were perceived to be natural and harmless.

Doubting efficacy. Sometimes patients felt vulnerable, as if they were guinea pigs (24) trying one medication after another. They waited in anxious anticipation to see if a new medication would start working and found it difficult to cope with any delay of demonstrable effect. If patients were doing well, they questioned whether it was due to the medication, or if their disease had naturally stopped progressing.

Conflicting and confusing advice. Some patients felt they received insufficient or contradictory information from within and outside the rheumatology service. This lapse led to confusion, mistrust, and heightened medication concerns. For example, the patients’ pharmacist, family doctor, or other specialists raised concerns about their DMARD. They noted that the drug information leaflets contained more information than provided by their physician.

Prognostic uncertainty with changing treatment regimens. Patients were afraid of their arthritis worsening when they switched or stopped their DMARDs. Even when patients did well when taking their medications, they would worry about returning “back to square one” (21). Some patients taking biologic DMARDs noticed a dramatic worsening of symptoms when they stopped their medications during pregnancy or infections, or for surgery.

Powerful social influences. “I feel I have a good doctor, and I feel that he was doing what was best for me personally. If it wasn’t for the trust I have in my doctor, then no, I wouldn’t have took it” (25). This theme describes how others,

including family, friends, doctors, and nurses can strongly influence the experience and perceptions of DMARDs in both positive and negative ways.

Swayed by others' experiences. Experiences of others taking DMARDs could influence patients' acceptance of DMARDs. One patient's mother developed gastrointestinal hemorrhage, and another patient's colleague took a day off work after taking methotrexate, and the patient cited these as reasons for never wanting to take methotrexate. In contrast, some patients were motivated to take medications by family members with arthritis who accepted and coped well with their DMARD, and from seeing older family members who had developed deformities and disability without DMARDs.

Partnering with physicians. Certain characteristics of the physician and their communication could influence patients' perceptions and attitudes toward DMARDs. Patients had confidence in physicians who were knowledgeable and optimistic, acknowledged their fears and needs, and provided a range of treatment options. These physicians made patients feel hopeful and secure in their treatment choices. Information from their physician that was consistent with other sources (e.g., internet, drug information leaflets) was regarded as credible. Some patients valued shared decision making, while others preferred to relinquish their decision to their doctor who they trusted.

Maintaining roles. Being able to function in the family role as a parent or grandparent could be the main reason for patients to take DMARDs. Others wished to maintain work roles and independence, or had a general goal to be healthy and normal and live the life they had before (26). For some, side effects from DMARDs impeded their ability to fulfil these roles and would lead to DMARD discontinuation.

Confidence in comprehensive and ongoing care. Patients felt secure with the frequency of followup in the biologic-agents clinic and in the setting of clinical trials for intensive conventional DMARD therapy. The practical and psychosocial support that nurses provide during regular biologic DMARD infusions and clinic visits and over the telephone created positive experiences. In contrast, some patients with ankylosing spondylitis found followup in the biologic-agents clinic unnecessary and inconvenient.

Valuing peer support. Patients valued the opportunity to share experiences with others with the same illness while receiving intravenous biologic-agent therapy. Some developed close friendships and considered their infusions to be a social outing.

Privilege and right of access to biologic agents. "You sit there and try and get every single drop out of, and then you make sure that the syringe, you really press it and try to squeeze the bit down to make sure you've got every drop. But it does...I mean it is precious because it's expensive" (27). This theme describes unique attitudes and perceptions of patients towards biologic DMARDs. The expense and restricted access to these medications created a sense of privilege for some, but could also invoke anger, guilt, and fear of being denied or losing access.

Expensive medications must be better. Patients felt privileged to have access to biologic DMARDs as they were

"horribly expensive" (27), and they were careful not to waste the medication when self-injecting.

Right to receive a biologic agent. Patients defended their right to receive a biologic agent and were angered if they did not meet the clinical requirements. They argued that they paid national insurance, and that there was a long-term economic benefit as surgery and hospitalizations would be reduced. Patients who qualified for a biologic agent felt guilty that others could not access these medications.

Fearing dispossession. Once receiving biologic agents, patients felt the medications were valued possessions and were afraid that they would be deprived of them. Some avoided telling the doctor or nurse of side effects, in case they were taken off their biologic agent.

Maintaining control. "Let me have the choice that I want to be treated aggressively. Don't take that away from me" (28). This theme describes the desire of patients to be in control of the decision to take DMARDs and to choose a DMARD based on life priorities. Patients also emphasized the importance of maintaining disease control, occasionally despite significant medication side effects.

Complete ownership of decision. Patients advocated their right to make the final decision about taking biologic and conventional DMARDs and wanted comprehensive information, including alternative treatment options. They urged physicians to be explicit about the potential effects of DMARDs on the body, including recognition that DMARDs were different from other medications that were perceived to be safer.

Taking extreme risks. Patients wished to remain in control of their disease and were willing to accept the risks of complications such as organ damage or low platelet counts to remain on their medications. Some ignored instructions to stop their medication. When DMARDs were highly effective, patients described them as something they would "kill for" (29).

Minimizing lifestyle intrusion. Patients wanted to control their choice of DMARD in order to minimize the impact on their day-to-day life. They wanted information that would better inform their decision making. For example, they wanted to be informed of the need to limit their alcohol intake, the timing of methotrexate dose to decrease side effects at work, and the impact of their DMARD on sexual function. Some patients preferred subcutaneous to intravenous biologic agents, because they could take the drug at home with minimal disruption to their routine.

Negotiating treatment expectations. "I mean I was, you know, really hoping against hope that it would work, having been on, sort of, most of the other conventional drugs and thinking well 'If this doesn't work, then what?'" (30). Patients' emotional response to their DMARD varied widely between joy, disappointment, and hopelessness, and depended on their initial and ongoing expectations of their medications.

Miraculous recovery. Patients were surprised and delighted if DMARDs exceeded their expectations and led to rapid and dramatic improvements, particularly with tumor necrosis factor inhibitors. Some patients felt "the healthiest

I've been in years" (30) and described forgetting they had arthritis. One patient described methotrexate as "the elixir of life" (29). These DMARDs elevated their mood, self-esteem, and relationships with their spouses and children.

Mediocre benefit. Other patients noted moderate improvements with DMARDs but still had disease flares, needed to use corticosteroids, and had functional limitations. Some accepted this and hoped for future medical advances. Others felt disappointed, as they were expecting an immediate and pronounced response to DMARDs.

Reaching the end of the line. Failing multiple DMARDs had a detrimental psychological and emotional impact on patients who felt increasing desperation. Patients felt they had reached the end of the line when given the option of biologic-agent therapy and saw these DMARDs as their last hope. They subsequently feared that if biologic agents did not work, they had no other options.

DISCUSSION

Dependence on DMARDs exacerbated disease identity in patients with rheumatoid arthritis and spondyloarthritis. They were alarmed about potential side effects, uncertain of treatment efficacy, and confused when they received conflicting medical advice. Concerns were alleviated through trust, confidence, and support in their health environment and positive experiences of family and friends. An immediate benefit or response to DMARDs was seen as a miracle, whereas others felt disappointed and hopeless from failed responses to DMARDs. The high cost and limited accessibility of biologic DMARDs increased their value.

Some experiences and perceptions were unique to biologic DMARDs. Patients felt well, supported by frequent biologic-agents clinic visits, nursing assistance, and peer support during infusions. Extending these positive experiences to conventional DMARD patients may improve their DMARD experience. Biologic DMARD patients may also experience rapid and dramatic treatment benefits and can feel privileged to receive restricted medications. However, regardless of the type of DMARD, arthritis, age, sex, and duration of disease, patients had similar concerns of DMARD toxicity, loss of efficacy, and desires to maintain control of their disease and social roles. Additionally, patients taking either type of DMARD desired to have control of the decision to take their medications and reported experiences of mediocre benefits or recurrent failures.

Our review has shown that patients believed DMARDs increased mortality, risk of cancer, and organ damage, despite evidence that cardiovascular disease and mortality may be reduced with the use of methotrexate and biologic DMARDs in rheumatoid arthritis (31,32). Explaining these benefits may help increase acceptance and reduce fears of long-term toxicity.

This study highlights the critical role of the patient-provider relationship in DMARD acceptance. By remaining optimistic and knowledgeable, validating patients' fears, and understanding their practical needs, physicians can foster a trusting and more successful therapeutic relationship with their patient. Communicating potential benefits and harms of medications by using examples of other patients' experiences may improve patients' understanding.

Communication also needs to be consistent between health professionals. Referring to reliable online resources may help patients feel more confident in treatment recommendations. A meta-analysis of 21 studies involving training physicians in communication skills found that all studies improved adherence (33). The use of decision aids may also improve knowledge, reduce decisional conflict, and increase participation in decision making (34).

Clinicians are encouraged to follow international guidelines that recommend the early use of DMARDs, and escalating or changing treatment to aim for a target of remission or low disease activity (5,6,14,35). However, patients can find commencing DMARDs at the first consultation alarming, and fear changes and escalations of therapy. This therapeutic approach may be more acceptable if patients understand that treating early and treating to target increases DMARD efficacy and results in better long-term outcomes.

A structured approach may help the clinician discuss DMARD use. The 5A approach (ask, assess, advise, assist, arrange followup) to smoking cessation has been adapted to guide brief counseling interventions targeting diet and exercise (36,37). We suggest the following 5A approach to address DMARD adherence (Figure 3). Ask about patients' experiences of their DMARDs, their concerns (especially those they may not mention, such as mortality, cancer, and organ damage), and goals (which could be to take fewer medications). Assess their willingness to take DMARDs. Advise on the benefits of DMARDs (using examples, include benefits on mortality, on maintaining roles, and control of disease), options (including practical implications to lifestyle), and communicate with optimism and consistency (referring to reliable internet sources and drug information leaflets). Assist patients taking DMARDs so they feel supported (including nursing, phone, and peer support). Arrange adequate followup and continue to address the above at every stage of their disease.

Similar barriers and facilitators to medicine taking have been identified in other chronic conditions (16,38). The perception of medicines as poison was identified in systemic lupus erythematosus (39). Fear of medication dependence

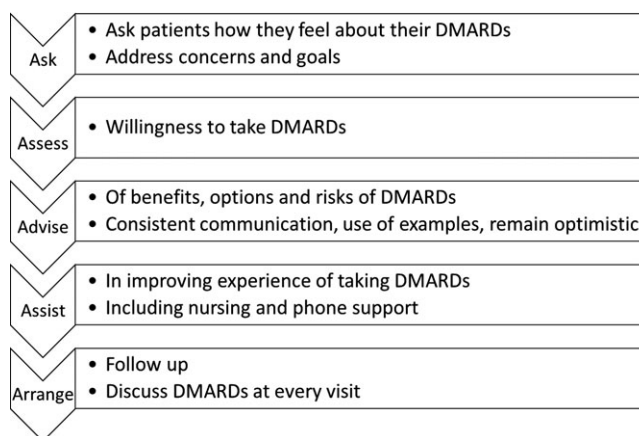


Figure 3. Proposed 5A approach to addressing disease-modifying antirheumatic (DMARD) drug use.

and long-term side effects were identified with antihypertensives and proton pump inhibitors (16). Medication non-adherence as a means to deny illness was reported with antiretroviral therapies and psychotropic medications (16). Patients with cancer doubted the efficacy of their medications (40). Patients with HIV were positively influenced by trustworthy health care providers and favorable experiences of others, and were motivated to take medications to maintain social roles (41,42). Unique experiences in relation to biologic DMARDs and specific ways to address barriers in our population are derived from the qualitative studies in our review.

Core themes relating to prescribed medications have been described by Horne et al using a necessity-concerns construct and by Azjen using the theory of planned behavior (43,44). The necessity-concerns cognitive representation includes beliefs about the necessity of medications, and beliefs about concerns, including long-term toxicity, disruptive effects of medication, and the danger of dependence. The theory of planned behavior postulates 3 independent determinants of intention and behavior. The first is attitude toward the behavior and refers to a person's favorable or unfavorable evaluation of the behavior. The second is subjective norm and refers to perceived social pressures to perform the behavior. The third is perceived behavioral control and refers to the perceived ease or difficulty of performing the behavior. Our study adds a broad and in-depth understanding into the beliefs of necessity and concerns, attitudes towards medication taking behavior, and the positive and negative social pressures that influence adherence in rheumatoid arthritis and spondyloarthritis.

Multiple researchers have independently assessed the transparency of reporting and triangulated findings during thematic analysis. Software was used to code the data to ensure a systematic and reproducible methodology. Our study has some limitations. While we provided contextual details for the data (if reported), we acknowledge the potential for decontextualization of the original data. Most studies were performed in high income countries with English-speaking participants with rheumatoid arthritis. The type of DMARD was not recorded in half the studies. This background highlights the need for qualitative studies to specify the type of DMARD and explore perspectives in non-English-speaking and spondyloarthritis patients. Successful interventions to improve DMARD adherence are needed. Exploring patients' ideas on how to improve their experience and perceptions of DMARDs may guide future interventions.

DMARDs are perceived as strong medications with frightening side effects. However, trust and security in medical care, positive DMARD experiences of others, and the ability to maintain social roles can motivate patients to use DMARDs. The physician is in a unique position to acknowledge and address fears of DMARD toxicity and adjust DMARD regimes to suit individual beliefs, lifestyles, and goals. The 5A approach to DMARD adherence may help structure discussions and combat barriers to medication taking. Understanding, supporting, and remaining optimistic for patients using these long-term medications can improve DMARD experience, with an aim to promote quality use of medicines and maximize the benefit patients can gain from their DMARDs.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Kelly had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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