Universität Basel

Medizinische Fakultät
Departement Public Health

SQUEEZE

25 Years of Growth
2000-2025
Nursing Science
Pflegewissenschaft
Universität Basel

Effectiveness and Implementation of Disease-Modifying Antirheumatic Drugs (DMARDs) Adherence Interventions in Rheumatoid Arthritis: A Systematic Review

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INTRODUCTION

Nonadherence to disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) is substantial[(1)] and associated with poor clinical outcomes[(2)].

Latest reviews do **not** include most **recent** studies, lack focus on methodological **quality**, aspects for **implementation** and are not embedded in the recent **taxonomies** to describe DMARD adherence-enhancing interventions[(3)].

AIM

To summarise the evidence of DMARD adherence-enhancing interventions in adult patients with RA in view of:

- Methodological quality
- Intervention components
- Intervention effectiveness
- Implementation-relevant content

METHODS

Design. Systematic review (PROSPERO CRD42024551854)

Databases. PubMed, CINAHL, Embase, PsycINFO

Inclusion criteria. 1) adult RA patients; 2) interventional studies testing adherence to DMARDs; 3) published since 1998; 4) in Czech Dutch, English, French, German, Italian, Portuguese, Spanish

Exclusion criteria. 1) healthcare provider-initiated changes; 2) no original results; 3) not-peer-reviewed; 4) no full text

Quality assessment. Adapted Risk of Bias instrument for Interventional Adherence Studies[(4)]

Intervention components. Behaviour Change Techniques[(5)]

Effectiveness outcomes. DMARD adherence; clinical; economic; other outcomes

Information relevant for implementation. Adapted Peters' criteria[(6,7)] enriched by the Basel Heptagon of Implementation Science[(8)] (see first column Table 2).

RESULTS

Out of 8.904 titles/abstracts screened, we included **25 studies**.

Eighteen (72%) studies were randomised controlled trials, six (24%) quasi-experimental, and one (4%) interrupted time series study.

In total, 23,930 (range 17-17,371) participants with a mean age of 46-63 years (61-100% female participants) were included.

Risk of bias was critical in 15 (60%), high in four (16%) and moderate in six (24%) studies. No study had a low risk of bias.

Table 1. *Impact of DMARD adherence-enhancing interventions on adherence*

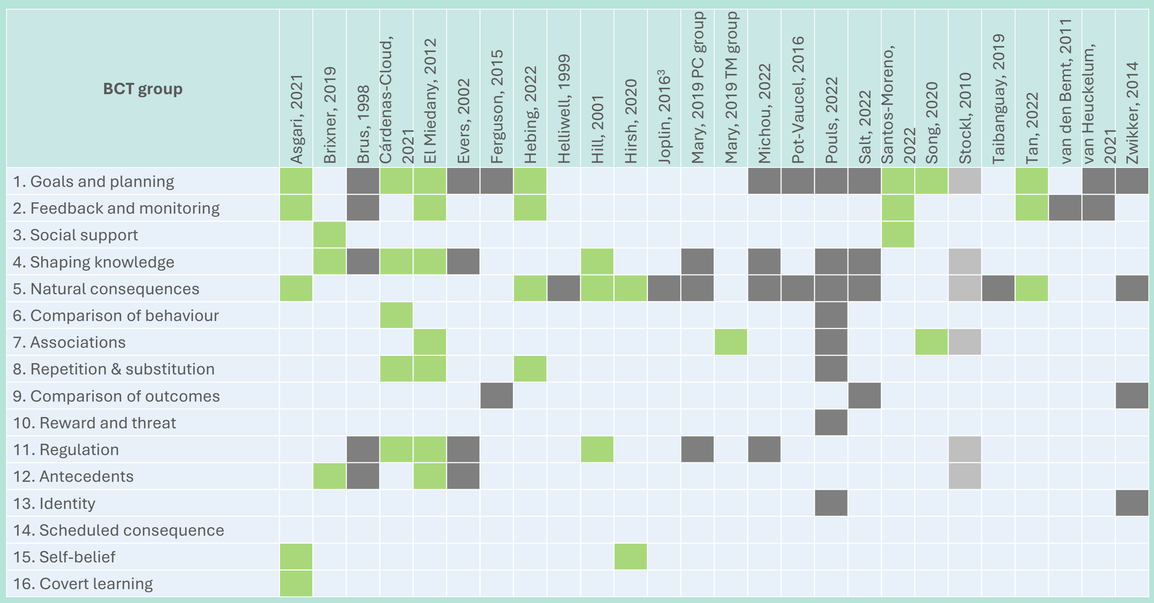

Table 2. *Implementation information 6,7 described in DMARD adherence-enhancing intervention studies in RA*

Implementation-relevant information	Asgari, 2021	Brixner, 2019	Brus, 1998	Cárdenas-Cloud, 2021	El Miedany, 2012	Evers, 2002	Ferguson, 2015	Hebing, 2022	Helliwell, 1999	Hill, 2001	Hirsh, 2020	Joplin, 2016	Mary, 2019	Michou, 2022	Pot-Vaucel, 2016	Poulds, 2022	Salt, 2022	Santos-Moreno, 2022	Song, 2020	Stockl, 2010	Taibanguay, 2019	Tan, 2022	van den Bemt, 2011	van Heuckelum, 2021	Zwikker, 2014
Transdisciplinary team	NR	NR	NR	NR	+	NR	NR	NR	NR	NR	+	NR	+	+	+	+	+	+	+	+	NR	NR	+	+	NR
Implementation science TMFs	-	-	-	-	-	-	-	NR	-	NR	-	-	-	NR	-	-	-	-	-	-	-	-	-	-	+
Context	-	-	-	-	+	(+)	-	-	-	-	-	-	-	-	(+)	-	-	(+)	-	-	+	-	-	-	-
Stakeholder involvement	NR	-	NR	-	NR	NR	+	+	NR	-	-	NR	NR	+	NR	+	NR	NR	+	-	-	-	-	+	+
Implementation strategies	NR	-	-	-	-	-	-	-	NR	-	+	-	NR	NR	+	-	-	-	-	-	-	-	-	NR	-
Implementation outcomes	+	NR	-	-	-	+	-	-	NR	-	+	-	+	NR	+	+	+	-	-	-	-	+	+	+	+
Process evaluation	-	NR	-	-	+	+	+	-	NR	-	+	-	-	-	-	-	NR	-	-	-	-	-	-	-	NR
Feasibility / pilot study	-	-	-	+	-	-	+	-	-	-	+	+	-	NR	-	-	-	-	-	-	-	-	-	-	-
Hybrid / implementation design	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Real-world setting	-	+	-	-	+	NR	-	+	+	+	+	-	+	+	-	+	+	+	+	+	NR	-	+	+	-
Sample representativeness	NR	+	-	-	NR	NR	NR	+	+	+	+	-	+	+	NR	+	NR	+	+	+	+	NR	+	+	-

One study had two intervention arms, so **26 interventions** were performed. A total of 113 Behavior Change Techniques were applied (range 1-9/study), most often:

- Information about health consequences (n=15, 57.7%)
- Problem solving (n=13, 50%)
- Instruction on how to perform behaviour (n=11, 42.3%)

Eleven (42%) interventions had a **positive effect on MA** (Table 1).

Only one of 16 (6%) interventions evaluating the impact on **disease activity** found a **positive effect**.

Quite limited **information relevant for implementation** was reported (Table 2):

- **Most reported criteria:** Evaluation in real-world setting (n=15, 60%), stakeholder involvement (n=14, 56%), sample representativeness (n=14, 56%)
- **Least reported:** Implementation science theories (n=1, 4%), hybrid/implementation designs (n=1, 4%), implementation strategies (n=2, 8%)

CONCLUSIONS

- In general, evidence on DMARD adherence-enhancing interventions is
- of **poor methodological quality**.
- Interventions mainly include a **limited range of Behavior Change Techniques** without reflecting recent evidence on effective behavioural strategies from MA research.
- There was a **positive effect on MA in less than half of the interventions** and almost never on disease activity; yet, it was limited by methodological caveats.
- Studies include **very limited information** that can guide subsequent **implementation in real-world settings**, highlighting the need for implementation science approach.

REFERENCES

1. Murage MJ et al. Medication adherence and persistence in patients with rheumatoid arthritis, psoriasis, and psoriatic arthritis: a systematic literature review. Patient prefer adherence 2018; 1483-503
2. Li L et al. Medication adherence has an impact on disease activity in rheumatoid arthritis: a systematic review and meta-analysis. Patient prefer adherence 2017; 1343-1356
3. MacIver A et al. Tele-health interventions to support self-management in adults with rheumatoid arthritis: a systematic review. Rheumatol Int 2021; 41(8):1399-418
4. Sinnappah K A et al. Risk of bias tools for medication adherence research: RoBIAS and RoBOAS. B J Clin Pharmacol 2025
5. Michie S et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann behav med 2013; 46(1):81-95
6. Peters DH et al. Implementation research: what it is and how to do it. Bmj 2013;347
7. Zullig LL et al. Moving from the Trial to the Real World: Improving Medication Adherence Using Insights of Implementation Science. Annu Rev Pharmacol Toxicol 2019; 59(1):423-45
8. De Geest S et al. Powering Swiss health care for the future: implementation science to bridge "the valley of death". Swiss Med Wkly 2020; 150:w20323

ACKNOWLEDGEMENT

We thank the SQUEEZE work package 8 members for their critical feedback on the study methods.

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Project funded by

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Swiss Confederation

Federal Department of Economic Affairs, Education and Research EAER
State Secretariat for Education, Research and Innovation SERI

Funded by the European Union

UK Research and Innovation

This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement no. 101095052, by UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee grant number 10055567 as well as the Swiss State Secretariat for Education, Research and Innovation (SERI). Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or any other granting authority. Neither the European Union nor any other granting authority can be held responsible for them.