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Biologic and Targeted Synthetic DMARDs Combined with Exercise Therapy in Rheumatoid Arthritis: A Scoping Review of Synergistic Effects and Functional Outcomes

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ABSTRACT

Rheumatoid arthritis is a long-term illness where medicines that change the course of the disease lower inflammation and stop damage from happening while exercise helps with being out of shape, weak muscles, trouble moving and heart problems. It is not clear if medicines that work on the system and exercise together have better results than either one on its own. To gather information about using medicines that change the course of the disease and exercise together for adults with rheumatoid arthritis focusing on how the disease is active how well they can move, pain, tiredness, how much they take part in life and safety. This paper uses a way of looking at all the information called a scoping review. It brings together guidelines and published information about medicines, exercise and studies that look at both together. The draft does not say that a full search of all information has been done; the final people who write the paper should do the search check the information and record what they find before they submit it. There is evidence that exercise works with regular care for rheumatoid arthritis especially for heart fitness, muscle strength, how well they can move and parts of feeling good. A study that looked at exercise with medicines found results on how active the disease was: some studies said the combination was better others showed no big difference and the way the studies were done stopped clear conclusions about a good combination. There is not information that is split up by the type of medicine. Exercise should usually go with not take the place of, medicine that tries to get the disease under control. The idea that exercise and the newer medicines work better together needs studies with clear plans for checking this standard way to plan the exercise and important results that matter to people.

Keywords: Activity; Rehabilitation; Ability to Function; Inflammatory Arthritis; Results of Treatment

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INTRODUCTION

Rheumatoid arthritis (RA) is a disease where the body attacks itself and causes swelling, pain, stiffness, tiredness and if not controlled damage to joints and losing the ability to move. The problems go beyond joints: weaker muscles, trouble with heart fitness changes in body shape, trouble sleeping, heart risks and less ability to work or take part in social activities may still happen even when the disease is not active. Medicine and physical therapy deal with related parts of health.

Medicines that change the course of the disease are very important for RA treatment. The usual ones like methotrexate are often the choice while medicines that work on the immune system and newer ones are used based on how active the disease is, how bad it might get how they respond, other health problems and what the patient wants. These medicines target parts of the immune system. Current ways of treating RA use checks and changes in medicine to get the disease under control while also considering the safety of each medicine.

Exercise is part of the care, not a substitute for medicine. Different kinds of exercise can help with being out of shape, weak muscles, trouble moving and general health. Guidelines say physical activity is a part of care for people with this kind of arthritis and another group says doing regular exercise is a good idea as part of a full approach. Exercise should be planned based on the persons condition, how joint damage they have other health problems, pain, tiredness, access to help and what they want to achieve.

The idea that combining medicine and exercise could be better makes sense biologically. In real life. Good medicine might reduce pain and inflammation enough to make it easier to exercise. Exercise might help with strength, heart fitness, confidence and taking part in life beyond what just controlling inflammation can do. Just because it makes sense doesn't mean it actually works better. A group that did a study found results with some studies saying the combination was better and others not showing much difference and the way the studies were done made it hard to say for sure. This is especially important for the medicines where there is not much evidence about exercise.

This review wants to find out what is known what is not clear and how doctors and researchers can look into the ways to use the newer medicines and exercise. The main questions are: (i) what types of exercise have been studied with the medicines; (ii) what results have been reported; (iii) what evidence shows that combining them is better; and (iv) what gaps in knowledge should be looked at next.

METHOD

Review design and reporting framework

A way of looking at all the information is right because the evidence covers different medicines, types of exercise study types, results and situations. The final review should be written according to a checklist. Should clearly show what is being mapped and what is not. This draft is based on what's known, not a full search and check.

Review question and eligibility framework

The way of looking at the problem is as follows: People with RA; Exercise or planned physical activity given with the medicines and usual medicine studies if they help the bigger question; Settings like outpatients, inpatients, community, home-based or supervised. The studies that can be included are those with planned and not planned studies, observations and guidelines. Writings without data can help with background. Are not counted as main evidence.

Search strategy to complete before submission

To make the final review repeatable, search MEDLINE/PubMed, Embase, CINAHL, Scopus or Web of Science and the Cochrane Library from the beginning to the search date. Look into study registries for not yet published studies. Use words that describe rheumatoid arthritis, the newer medicines and exercise. Check the references of included studies and relevant reviews.

Example search on PubMed (adjust and check for each database): ("Arthritis, Rheumatoid"[Mesh] OR rheumatoid arthritis[tiab]). Biologic DMARD*[tiab] OR biological DMARD*[tiab] OR targeted synthetic DMARD*[tiab] OR tsDMARD*[tiab] OR bDMARD*[tiab] OR Janus kinase inhibitor*[tiab] OR disease-modifying antirheumatic drug*[tiab]). Exercise[mesh] OR exercise therap*[tiab] OR physical activit*[tiab] OR resistance training[tiab] OR aerobic training[tiab] OR rehabilitation[tiab]).

Selection, charting and synthesis

Two people should check the titles and abstracts and full texts solve disagreements by talking or a third person and record why they are not included. Record study type, country, number of people features, medicine type and exposure exercise type and how much, comparison follow-up, results, side effects how well people followed the plan and main results. A tested form should be used. Since the question is about the range and type of information the main way of looking at the results should be descriptive and thematic not a summary. If they do a check they should say what tool and why. It is not required for every scoping review.

Outcomes of interest

Results include how active the disease is, markers of inflammation, pain, tiredness, how well they can move, muscle strength, heart fitness, range of movement taking part in life feeling good work results how well people followed the plan, flare-ups, injuries and serious side

effects. Where reported results should be split by the type of medicine. Whether exercise was done with supervision at home or a mix.

Evidence Map and Results Synthesis

thing to note: the sections below summarize what is known and advice from experts, not the results of a new full search. A complete review must list the search date how many records were found how many were removed how many were checked how many were looked at and how many were included. These numbers must come from the authors work. Not be guessed.

Medicines and the role of treatments

The goal of medicines is to lower inflammation stop damage and keep function. The 2022 guidelines and recommendations say medicine is part of a plan that includes making choices with the patient and managing other health problems. The newer medicines include those that target parts of the system; the other newer medicines include small molecules that stop parts of the bodys signals. These groups are different in how they work how they are given, their safety and the people they are used for.

Controlling the disease with medicine can help with treatment by lowering pain, stiffness and active inflammation. Even if the disease is under control, muscle mass, heart fitness confidence with moving and taking part in life after being inactive may not come back. Ongoing pain, tiredness, damage, to joints, heart health problems and fear of making symptoms worse may still stop people from being active. So medicine and exercise should be seen as parts that work together.

Exercise modalities and functional outcomes

Aerobic training includes activities like walking, cycling and aquatic exercise. These are movements designed to boost cardiorespiratory fitness and endurance. Resistance training focuses on building muscle strength and power. This kind of strength can decline due to inflammation, lack of movement, pain avoidance or aging. Flexibility and range-of-motion exercises help with limitations in movement. Balance and neuromotor training can be especially helpful for people with lower-limb issues. Who are at higher risk of falling. Combined programmes often mix types of exercise and include tasks that relate directly to daily life activities.

Evidence-based guidelines support physical activity for people with inflammatory arthritis. Exercise should be adjusted to the individual. Increased slowly based on tolerance [3,7]. The ACR guideline conditionally recommends exercise for rheumatoid arthritis. It stresses that the kind and amount of exercise should be chosen with the patient through shared decision-making [4]. Studies on exercise vary a lot in frequency, intensity, how long they last, supervision and support for sticking with the programme. This difference makes it hard to

compare results directly. It also makes it difficult to find one programme that works for all patients.

Functional outcomes should be measured directly not guessed from markers. A drop in DAS28 does not mean there is an improvement in walking ability, hand function or fatigue. On the hand someone might get stronger and more active even if their disease activity stays mostly unchanged. That is why a full multidomain assessment is important when looking at treatments.

Evidence on exercise and antirheumatic medication

The most relevant evidence review found 11 studies that looked at exercise combined with antirheumatic medication. In the comparisons between groups, six out of ten studies did not find a difference in DAS28 components between the exercise-plus-medication group and the medication-only group. Four studies reported disease activity outcomes in the combined group. However the review pointed out study sizes, methodological weaknesses and a high risk of bias across many areas. It concluded that any combined effect on disease activity is still uncertain [5].

These results must be interpreted carefully. First not finding a difference between groups does not prove that the two groups are equal especially when the studies are too small to find real effects. Second finding a result in the combined group does not prove synergy. That would only be true if the study design could separate the effects of exercise and medication from their effect. Third DAS28 components do not represent what matters most to patients. Outcomes like fatigue, strength, daily activity levels and quality of life are more meaningful. Fourth the evidence was not strong enough to draw conclusions about whether bDMARDs or tsDMARDs respond differently to combined treatment.

The reasonable conclusion is not balanced. The benefits of exercise for fitness, strength and some aspects of function are supported by a body of evidence, in rheumatoid arthritis and inflammatory arthritis. The idea that exercise enhances the disease-modifying effect of bDMARDs or tsDMARDs has not been proven. Future studies need to distinguish between added functional benefits and a true interaction affecting inflammatory disease activity.

Functional outcomes: current interpretation

Outcome domain	What current evidence supports	Interpretive caution
Disease activity	Some combined-treatment studies report improvements; others do not show significant between-group differences [5].	Direct synergy with advanced DMARDs remains unproven; distinguish within-group change from between-group effects.
Physical function	Exercise can support functional capacity as part of comprehensive RA care [3,4].	Function depends on joint damage, pain, fatigue, comorbidity, and baseline

		deconditioning, not inflammation alone.
Strength and aerobic fitness	Resistance and aerobic training target measurable deficits and are supported in physical-activity guidance [3,7].	Training dose, adherence, supervision, and outcome tests vary across studies.
Pain and fatigue	Exercise may improve symptoms and broader health outcomes, although response is heterogeneous [7].	Flare, overtraining, sleep, mood, and concurrent treatment can affect reported symptoms.
Quality of life and participation	Potential gains extend to daily activity and social participation.	Studies should include validated patient-reported measures and longer follow-up.
Safety	Individualized exercise is generally incorporated into recommended RA care [3,4].	Report flares, injury, cardiovascular events, medication-related infection risk, and withdrawals explicitly.

Potential mechanisms of synergistic effects

I believe several mechanisms might explain complementary effects but we must treat them as hypotheses until we test them directly. If synovitis goes down movement becomes more comfortable. We can load the joint gradually. Resistance exercise can counter muscle weakness. Boost a person's ability to do daily tasks. Aerobic training can raise cardiorespiratory fitness and tackle health risks that are not fully fixed when joint inflammation is suppressed. Structured rehabilitation can also raise self-efficacy, pacing and confidence which helps people stick to activity.

Exercise can influence metabolic, neuroendocrine and inflammatory pathways. However these changes do not automatically mean that exercise makes a specific biologic or targeted synthetic agent work better. To show a mechanistic interaction we need biomarker and clinical data that come from a study designed to separate treatment effects. In talk calling the result a 'complementary benefit' is safer than saying 'synergy' unless we have proven an interaction.

Safety and tailoring of exercise in people receiving advanced DMARDs

I start exercise planning by checking disease activity, joint stability and damage cardiovascular risk, other illnesses, current physical capacity past exercise experience and what the patient prioritises. If there is synovitis, a recent injury, unstable heart symptoms or big functional decline we may need to pause or change the plan and review it with a clinician. Low-impact aerobic options, water-based activities, slow resistance progression and joint-protection strategies can fit each person's needs.

Medication-related considerations are important. Should not make us stop exercise entirely. Clinicians need to think about infection risk, low blood counts or other drug-specific side

effects, heart and clot risks linked to agents and advice for surgery or acute illness. Patients should be told to report any worsening swelling, odd pain chest problems, heavy breathlessness, fever or other scary symptoms. A physiotherapist or qualified exercise professional who works with the rheumatology team can help adjust the programme.

Practical model for care

I see a pragmatic care pathway that starts with treat-to-target medication and a baseline check of function and activity. Then the clinician and patient agree on exercise goals pick the right aerobic and resistance activities and set how often how hard, how long and what type of exercise. A little supervision can help people who have disability, fear of moving or many other health problems. We should review progress with disease activity, symptoms, how well the patient sticks to the plan and any side effects. We should change the plan of stopping it when symptoms change.

The following is a proposed framework, not a validated algorithm:

1. Assess disease control and safety.
2. Document baseline function and patient goals.
3. Pick aerobic, resistance, mobility and balance parts.
4. Start at a dose and progress slowly.
5. Watch adherence, symptoms, function and safety.
6. Work with the rheumatology and rehabilitation team to coordinate changes.

DISCUSSION

I see this evidence map showing a difference between two questions that people often mix up. The first question is if exercise helps people with RA who are taking DMARDs. The guidelines and the bigger evidence say that exercise is part of care especially for fitness, strength and daily function. The second question is whether exercise together with DMARDs gives a stronger effect on the inflammation that drives the disease. A scoping review that looked at this found mixed results and weak methods so we still do not know the answer.

The difference matters for care. I do not want patients to wait for synergy data before getting good exercise advice. At the time doctors and scientists must not say that exercise makes a specific biologic or targeted synthetic drug work better if we do not have clear proof. The idea of integrated care is already solid because the treatments hit distinct health areas.

The literature has common limits. Studies are usually small exercise programmes vary a lot. We may not see how well patients stuck to the plan or how much training they actually did. Medication use may also be described briefly to judge how it changes the effect. Sometimes we focus on disease activity of function even though function is a main reason, for rehab.

Follow-up can be too short to see if people keep exercising how it affects work or long-term safety. If a study covers drug classes the subgroup comparisons might be too weak.

Another challenge is inference. A two-arm trial that compares exercise plus medication with medication can estimate the extra benefit of adding exercise under the conditions of the study. However it does not automatically show that exercise and medication work together on a level. A factorial design or a prespecified interaction analysis if it is possible and ethical is a way to test whether exercise and medication have a synergistic effect. Studies should also record any changes in medication during follow-up because increasing or reducing medication can confuse the results.

Implications for practice

Doctors can safely present exercise as a helpful part of RA care not as a replacement for medication. Exercise should be. Stepped up based on the person's symptoms, goals, ability, other illnesses and preferences. Outcomes should be checked in areas: inflammatory disease activity, pain, tiredness, strength, heart fitness, daily tasks, life quality and social participation. Shared decision-making and teamwork among rheumatology, physiotherapy and primary care can help people keep exercising for the term.

Priorities for research

Future studies should enroll enough participants clearly describe those who are taking biologic disease-modifying drugs or targeted synthetic drugs and report the drug class, how long the drug has been used any other conventional drugs, steroid use and any medication changes. Exercise programs should detail how often how long what type, how it progresses, who watches it how well people stick to it and any other help. Researchers should set one or more outcomes that matter most to patients and treat disease activity as an outcome instead of assuming it covers all benefits.

If the aim is to test synergy protocols should state the interaction goal and the statistical plan before the study starts. Trials should consider a factorial or another appropriate comparison design, split groups by disease activity and medication type and have enough follow-up to see if the effects last. Consistent reporting of side effects, flare-ups, drop-outs and reasons for not sticking to the program is essential. Qualitative research can uncover what stops. Helps people, especially those with tiredness, disability, limited access to rehab or financial limits.

Strengths and limitations of this draft

This draft brings together medication management, exercise recommendations, functional results and the small amount of evidence on using both together. It stresses the difference between a benefit and proven synergy. It is not yet a finished scoping review. A complete search of databases independent screening, charting of sources and a PRISMA-ScR flow

diagram have not yet been done. Therefore it cannot give a count of studies a full evidence map or claim that it covers everything. The final authors should finish these steps check all references and study details, against the papers and change the results accordingly. inflammatory disease activity.

CONCLUSSION

Exercise therapy is an important complement to pharmacological disease control in rheumatoid arthritis. Available guidance supports individualized physical activity to improve fitness, strength, and functional health, while the evidence that exercise specifically potentiates biologic or targeted synthetic DMARD effects on disease activity remains inconclusive. Integrated care should therefore be recommended for its complementary clinical value without overstating synergy. Definitive conclusions require rigorous trials with well-described medication exposure, reproducible exercise prescriptions, multidimensional outcomes, adequate follow-up, and prespecified analyses of interaction.

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