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CLINICAL TRIAL REPORT

Efficacy of Paroxetine as an Adjuvant Therapy in Rheumatoid Arthritis Patients: A Randomized Controlled Study

Khlood Mohammad Aldossary[1], Mahmoud S Abdallah[2,3], Esraa M Mosalam[3,4], Noha Kamal[2], Dalia S Saif[5], Sahar Abdel-Rahman Elsayed[6], Naglaa Afifi[7], Haitham G Zakaraia[2], Mohannad O Khrieba[8], Mostafa M Bahaa[8,9]

[1]Department of Pharmacy Practice, College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia; [2]Department of Clinical Pharmacy, Faculty of Pharmacy, University of Sadat City (USC), Sadat City, Menoufia, Egypt; [3]Department of PharmD, Faculty of Pharmacy, Jadara University, Irbid, Jordan; [4]Biochemistry Department, Faculty of Pharmacy, Menoufia University, Shebin El-Kom, Egypt; [5]Department of Rheumatology, Rehabilitation, and Physical Medicine, Faculty of Medicine, Menoufia University, Menoufia, Egypt; [6]Department of Rheumatology, Rehabilitation, and Physical Medicine, Faculty of Medicine, Sohag University, Sohag, Egypt; [7]Department of Internal Medicine and Rheumatology, Faculty of Medicine, Ain Shams University, Cairo, Egypt; [8]Pharmacy Practice Department, Faculty of Pharmacy, Horus University-Egypt (HUE), New Damietta, Egypt; [9]Pharmacy Practice Department, Faculty of Pharmacy, Mansoura National University, Gamasa, Egypt

Correspondence: Mostafa M Bahaa, Pharmacy Practice Department, Faculty of Pharmacy, Horus University, New Damietta, Egypt, Email mbahaa@horus.edu.eg; mostafabahaamnf@gmail.com

Background: Despite advances in pharmacological interventions for rheumatoid arthritis (RA), a subset of patients continues to experience disease activity, highlighting the need for adjunctive therapeutic strategies.

Objective: To assess the therapeutic efficacy of paroxetine when administered as adjuvant therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in patients with rheumatoid arthritis (RA).

Methods: In this randomized, double-blind, clinical trial, one hundred patients were randomized in 1:1 ratio to receive either csDMARDs including methotrexate plus placebo (control group) or paroxetine (paroxetine group). The primary endpoint was the change in Disease Activity Score using 28 joint counts (DAS-28) [Tender joint count (TJC), swollen joint count (SJC), C-reactive protein (CRP), visual analogue scale (VAS)] at three months. Secondary endpoints included multidimensional health assessment questionnaire [morning stiffness (MS), pain, fatigue, physical functioning (PF)].

Results: After treatment, both groups demonstrated significant within-group improvements in TJC, SJC, VAS, and DAS-28, with superior improvements observed in the paroxetine group ($p = 0.016$, 0.0006, 0.03, and 0.005, respectively). CRP showed no significant change in the control group ($p = 0.933$). Paroxetine group showed significant reductions in MS, pain, and fatigue ($p = 0.024$, 0.03, and 0.006, respectively) compared with the control group, while PF were significant within groups but not between groups ($p = 0.208$). Adverse events were comparable, except for a higher incidence of decreased libido in the paroxetine group.

Conclusion: Adjunctive paroxetine significantly improved clinical and patient-reported outcomes in mild and moderate RA patients and was generally well tolerated, supporting its potential as an effective adjunctive therapy. The relatively small single-center sample, the exclusion of severe RA patients, the short disease duration, the low seropositivity, absence of mental health assessment, the possibility of overlapping with secondary pain mechanisms (eg, central sensitization or early fibromyalgia features) may limit the generalizability of the findings to broader and more diverse patient populations.

Trial Registration Identifier: NCT06231745.

Keywords: rheumatoid arthritis, paroxetine, DAS-28, CRP, disease-modifying antirheumatic drugs, randomized controlled trial

Introduction

Rheumatoid arthritis (RA) is a long-standing autoimmune inflammatory disease marked by continuous synovial inflammation, which contributes to progressive cartilage and bone damage, eventually resulting in joint destruction.[1] Both inherited genetic factors and environmental exposures substantially contribute to the risk of developing the disease.[2]

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Additionally, several lifestyle and biological factors including diet, cigarette smoking, hormonal influences, alcohol consumption, gut microbiota, infections, and coffee intake have been implicated in the development and progression of RA.[2] Clinically, RA is frequently characterized by morning stiffness, pain involving the shoulder, neck, and pelvic girdle, impaired mobility, and systemic features including fever.[3]

Pathogenesis of RA involves a dysregulated immune response in which T cells, B cells, and pro-inflammatory mediators such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, IL-1, and IL-17 drive chronic synovial inflammation.[4] This process leads to pannus formation, bone erosion, and cartilage destruction. In addition to joint damage, systemic effects arise, including increased acute-phase proteins, anemia of chronic disease, cardiovascular complications, osteoporosis, fatigue, and depression.[5] Recent research has identified G protein–coupled receptor kinase 2 (GRK2) as a key regulator in RA pathogenesis.[6] Prolonged activation of the prostaglandin E2 (PGE2) receptor for human prostaglandin E2 receptor 4 (EP4) and M2 macrophage polarization recruits GRK2 to the cell membrane.[7] This reduces EP4 expression on the surface and alters signaling balance. GRK2 further contributes to RA by regulating fibroblast-like synoviocyte (FLS) proliferation and peroxisome proliferator–activated receptor gamma (PPARγ) signaling.[8] GRK2 also interacts with tumor necrosis factor receptor-associated factor 2 (TRAF2), enhancing TRAF2 ubiquitination and activating nuclear factor (NF)-κB signaling.[9] This cascade drives inflammation and joint damage. Inhibition or knock-down of GRK2 reduces synovial hyperplasia and FLS proliferation in experimental models, suggesting GRK2 as a potential therapeutic target in RA.[8,9]

Drug repurposing — the process of identifying new therapeutic uses for existing approved medications — has gained momentum as an efficient strategy to accelerate the development of novel treatments.[10] Compared with traditional drug development, repurposing leverages established safety, pharmacokinetics, and toxicity data, thereby reducing both time and cost.[11] This approach is especially attractive for chronic and immune-mediated diseases, such as RA,[12] where unmet needs persist despite advances in disease-modifying antirheumatic drugs (DMARDs) and biologics. Patients may still encounter suboptimal responses, high costs, or adverse effects, underscoring the need for additional therapeutic options that are safe, affordable, and mechanistically novel. This approach was successfully applied in various diseases.[13–17]

Paroxetine, a member of the selective serotonin reuptake inhibitor (SSRI) class, is reported in the literature as one of the most frequently prescribed agents for off-label use in routine clinical practice.[18] It showed promising results in previous studies as it mitigated arthritis in rats by inhibiting GRK2-mediated T cell activation and synovial infiltration, restoring T cell subset balance, suppressing pro-inflammatory cytokines and chemokines, and attenuating extracellular signal-regulated kinase (ERK) pathway signaling.[19–21] Paroxetine also exhibited significant anti-rheumatic effects in complete Freund's adjuvant–induced RA in rats by attenuating oxidative stress, inflammation, and apoptosis, while modulating receptor activator of nuclear factor-kappa B ligand (RANKL)/ osteoprotegerin (OPG) signaling pathways.[22] Paroxetine selectively inhibited GRK2 by binding to its active site thereby enhancing cardiac contractility in vitro and in vivo.[23] Biochemical and structural analyses showed paroxetine exhibits measurable affinity and up to 50-fold selectivity for GRK2 versus other GRKs, and that selectivity is related to conformational/adenine nucleotide interactions of GRKs.[24] These findings provide a strong rationale for investigating the therapeutic potential of paroxetine in RA patients receiving standard csDMARDs therapy. We hypothesized that paroxetine, when added to methotrexate, would provide superior clinical benefit compared with methotrexate alone, reflected in reduced disease activity and improved patient-reported outcomes.

The aim of this study was therefore to evaluate the efficacy and safety of adjunctive paroxetine therapy in patients with RA focusing on the change in Disease Activity Score using 28 joint counts (DAS-28), incorporating tender joint count (TJC), swollen joint count (SJC), C-reactive protein (CRP), and the visual analogue scale (VAS) and multidimensional health assessment questionnaire domains, specifically morning stiffness (MS), pain, fatigue, and physical functioning (PF).

Patients and Methods

Study Design

This was a randomized, double-blind, parallel-group clinical trial conducted to evaluate the efficacy of adjunctive paroxetine in patients with rheumatoid arthritis (RA). The trial was conducted between January 2024 and July 2025.

This trial was conducted at the Physical Medicine, Rheumatology, and Rehabilitation Department, Faculty of Medicine, Menoufia University. The RA service functions as a referral unit managing both newly diagnosed and established rheumatoid arthritis cases. Patients were screened and approached during routine outpatient clinic visits. Initial eligibility assessment was performed by trained rheumatology physicians not involved in randomization or outcome evaluation. The study aims, procedures, and potential risks were explained in a dedicated counseling room, and written informed consent was obtained from patients willing to participate. Participants were allocated in a 1:1 ratio to either the control or paroxetine group. The randomization sequence was generated using a computer-based block randomization method to ensure balanced allocation between groups. Concealment of allocation was achieved through the use of opaque, sealed envelopes, sequentially numbered and prepared by an independent statistician who did not participate in recruitment or assessment procedures. Both patients and investigators, including those responsible for clinical evaluation and statistical analysis, were blinded to treatment assignment throughout the study.

Inclusion Criteria

Eligible participants were adults between 23 and 57 years of age who met the 2010 American College of Rheumatology–European League Against Rheumatism (ACR–EULAR) classification criteria for RA and exhibited active disease, regardless of disease duration.[25]

Participants were permitted to continue stable doses of methotrexate (MTX), nonsteroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 inhibitors, acetaminophen, and low-dose oral corticosteroids. The administration of intravenous, intra-articular, or intramuscular corticosteroids, intra-articular hyaluronate sodium, biologic DMARDs, or additional csDMARDs was not permitted within four weeks prior to initiation of the study medication. If the patients were stabilized on combined csDMARDs for more than 4 weeks, they were allowed to be included in the study.

Exclusion Criteria

Patients were excluded if they declined to provide informed consent or had any of the following: diabetes mellitus, congestive heart failure, prior adverse reaction to paroxetine, current use of prednisolone >10 mg/day, receipt of biological DMARDs, severe anemia, active infection, clinically significant hepatic or renal impairment, pregnancy, or lactation.

Interventions

Participants were randomized into two groups:

Control Group (n = 50): Received csDMARD therapy consisting of methotrexate 7.5 mg/week intramuscularly for two weeks then 15 mg/week (Metoject® prefilled syringe, Medac GmbH, Germany) plus placebo tablet orally once daily.

Paroxetine Group (n = 50): Received csDMARD therapy consisting of methotrexate 7.5 mg/week intramuscularly for two weeks then 15 mg/week plus paroxetine 20 mg orally once daily (Paroxetine, Eva Pharma, October City, Egypt).

All patients received the same low-dose corticosteroid regimen (prednisolone 10 mg/day). Treatment duration was three months. Compliance was assessed by pill count and injection logs at each follow-up visit. Study medication and matching placebo were prepared and labeled by the hospital pharmacy and indistinguishable in appearance.

Study Outcomes

Primary Outcome

The primary efficacy endpoint was the change in disease activity score using 28 joint counts (DAS28) at three months. A DAS28 score >5.1 was classified as high disease activity, $3.2 < DAS28 \leq 5.1$ as moderate activity, $DAS28 \leq 3.2$ as low activity, and DAS28 <2.6 as remission.[26]

Secondary Outcome

The secondary endpoints were designed to provide a comprehensive evaluation of both clinical and patient-reported outcomes. Clinical secondary endpoints included changes in tender joint count (TJC), swollen joint count (SJC), C-reactive protein (CRP), and the visual analogue scale (VAS) for global disease activity. Patient-reported secondary

endpoints comprised morning stiffness (MS), pain intensity, fatigue severity, and physical functioning (PF), assessed using standardized questionnaires.

Joint counts and VAS assessments were performed by trained rheumatologists who underwent standardized training to ensure inter-rater reliability.

Safety assessments included the incidence and type of adverse events, with specific attention to gastrointestinal disturbances, neurological symptoms (drowsiness, headache), and sexual dysfunction (decreased libido).

Study Follow-Up

Participants were closely monitored through weekly telephone check-ins and monthly in-person visits to ensure compliance with the study protocol, maintain patient safety, and track the progression of RA symptoms. At baseline, all participants underwent a comprehensive medical evaluation, including liver and kidney function tests, to exclude underlying organic conditions. All participants received standardized instructions at enrollment to ensure compliance and reliability of the study outcomes. Patients were advised to take their study medication (paroxetine or placebo) once daily at the same time, preferably in the evening, with a glass of water. They were instructed not to alter the dose, discontinue treatment, or initiate any new medications without prior consultation with the study physician. Patients were counseled to continue their background methotrexate therapy as prescribed and to maintain stable use of permitted concomitant medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors, acetaminophen, and low-dose corticosteroids. The use of biological DMARDs, additional csDMARDs, or intra-articular corticosteroid injections was prohibited during the study period.

To ensure accurate therapeutic assessment, patients were instructed to record daily symptoms in a study diary, including pain severity, morning stiffness duration, fatigue levels, and any unusual symptoms or side effects. They were also advised to promptly report any adverse events such as gastrointestinal disturbances, neurological symptoms (eg, dizziness, drowsiness, headache), or sexual dysfunction.

Participants were informed about the importance of attending all scheduled follow-up visits for clinical evaluation and laboratory testing. They were asked to refrain from using over-the-counter herbal remedies or dietary supplements targeting joint pain or inflammation during the trial.

Women of childbearing potential were instructed to use adequate contraception throughout the study, and all participants were reminded to avoid alcohol consumption in excess due to possible drug interactions and hepatotoxicity.

Adherence was reinforced through verbal counseling at each visit, and medication compliance was assessed by pill count and patient self-reporting in diaries.

Therapeutic Assessment

Therapeutic assessment was evaluated through: DAS-28 CRP and the Multidimensional Health Assessment Questionnaire (MDHAQ).

The Disease Activity Score based on 28 joint counts and C-reactive protein (DAS-28 CRP) is a validated composite measure that reflects overall disease activity in rheumatoid arthritis. By integrating clinical and laboratory parameters, it is highly sensitive to temporal changes and is therefore extensively applied in both clinical practice and research.[27] The DAS-28 CRP is calculated from four components: the tender joint counts out of 28 specified joints (TJC-28), the swollen joint counts out of the same 28 joints (SJC-28), the patient's global assessment of disease activity measured on a 0–100 mm visual analogue scale (VAS), and the serum C-reactive protein level (CRP, mg/L).[28]

The formula used is: $\text{DAS-28 CRP} = 0.56 \times \sqrt{\text{TJC-28}} + 0.28 \times \sqrt{\text{SJC-28}} + 0.36 \times \ln(\text{CRP} + 1) + 0.014 \times \text{VAS} + 0.96$.

The Multidimensional Health Assessment Questionnaire (MDHAQ) was employed as a patient-reported outcome measure to evaluate functional status and symptom burden in patients with rheumatoid arthritis.[29] The MDHAQ is an extension of the original Health Assessment Questionnaire (HAQ) and provides a broader evaluation of disease impact by incorporating several domains.[30] It includes physical function (PF), scored across 10 items assessing daily activities such as dressing, arising, eating, walking, and hygiene, with each item graded on a scale of 0–3 (0 = without difficulty, 1 = with some difficulty, 2 = with much difficulty, 3 = unable to do). Additional domains include numerical rating scales for pain, and fatigue, each scored from 0 to 10, where higher scores indicate more severe symptoms. Morning stiffness

(MS) is assessed based on its duration in minutes, providing additional clinical context. From these components. The MDHAQ is brief, taking approximately 5–7 minutes to complete, and has been validated for use in both clinical practice and research. In this study, it was administered at baseline and at three months to capture changes in morning stiffness, pain, fatigue, and physical functioning as secondary endpoints, providing a comprehensive assessment of the impact of adjunctive paroxetine therapy on patient-reported outcomes.

Ethical Considerations

The study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki and received approval from the Research Ethics Committee of the Faculty of Medicine, Menoufia University (8/2022 PMRR2-3). Written informed consent was obtained from all participants prior to enrollment, and the trial was prospectively registered at ClinicalTrials.gov (Identifier: NCT06231745).

Sample Size Calculation

The sample size was calculated using G*Power version 3.1, based on detecting a clinically relevant difference in DAS-28 scores between groups at three months. Assuming an effect size of 0.6, a power of 80%, and a two-sided alpha of 0.05, the minimum sample required was 45 patients per group. To account for potential attrition, 50 patients were enrolled in each arm (total = 100).

Handling of Missing Data

The analysis was conducted according to the intention-to-treat (ITT) principle. For participants who withdrew or were lost to follow-up, missing data were imputed using the baseline observation carried forward (BOCF) approach to maintain randomization integrity and minimize potential bias.

Statistical Analysis

Statistical analyses were conducted using GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA). The Shapiro–Wilk test was applied to evaluate the normality of continuous variables. For within-group comparisons, the paired Student's *t*-test was employed for normally distributed data, whereas the Wilcoxon signed-rank test was used for non-parametric data. Between-group comparisons before and after treatment were performed using the unpaired Student's *t*-test for parametric data and the Mann–Whitney *U*-test for non-parametric data. Quantitative variables were presented as mean ± standard deviation (SD) when normally distributed, or as median with interquartile range (IQR) when non-parametric. Qualitative variables were summarized as frequencies and percentages, with categorical data analyzed using either the Chi-square test or Fisher's exact test, as appropriate. Correlations were assessed using Pearson's coefficient for normally distributed data and Spearman's rank correlation for non-parametric data. All statistical tests were two-sided, with p-values < 0.05 considered statistically significant.

Results

Baseline Demographic and Laboratory Data

At baseline, there were no statistically significant differences between the control group (methotrexate + placebo, n = 50) and the paroxetine group (methotrexate + paroxetine, n = 50) with respect to demographic, clinical, or laboratory parameters (Table 1).

The mean age was comparable between groups (43.68 ± 13.89 vs 44.62 ± 14.67 years, $p = 0.742$). The sex distribution (male/female: 15/35 vs 18/32, $p = 0.523$), body weight, height, and BMI did not differ significantly. Similarly, baseline liver function tests (ALT and AST), serum creatinine, hemoglobin, white blood cell and red blood cell counts showed no significant differences between groups ($p > 0.05$ for all).

The median disease duration was 2 years (IQR 1–4) in the control group and 2.5 years (IQR 1–4) in the paroxetine group ($p = 0.754$). The proportion of smokers (28% vs 18%, $p = 0.234$) and rheumatoid factor positivity (40% vs 34%, $p = 0.534$) were similar.

Table 1 Clinical, Demographic and Laboratory Data of the Patients

Parameter	Control Group (n=50)	Paroxetine Group (n=50)	*p* value
Age (years)	43.68 ± 13.89	44.62 ± 14.67	0.742
Sex (M/F)	15 /35	18 /32	0.523
Weight (kg)	72.50 (60–82.25)	74 (62–82.25)	0.450
Height (m^2)	1.71 (1.62–1.83)	1.75 (1.66–1.85)	0.234
BMI (kg/m^2)	24.14 (20.92–23.61)	24.60 (21.34–24.66)	0.624
Serum ALT (IU/L)	41.74 ± 8.01	43.74 ± 5.80	0.156
Serum AST (IU/L)	45 (40–50)	43.50 (39–49.25)	0.641
SrCr (mg/dL)	1.055 (0.89–1.20)	1.115 (0.95–1.20)	0.290
Hgb (mg/dl)	13.21 ± 0.74	13.26 ± 0.72	0.766
WBCs (10^3)	6.074 ± 0.99	6.056 ± 1.04	0.922
RBCs (10^6)	5.188 ± 0.41	5.214 ± 0.24	0.759
Disease duration (year)	2 (1–4)	2.5 (1–4)	0.754
Smoking	14	9	0.234
Patients with positive RF	20	17	0.534
Mild cases	17	22	0.305
Moderate cases	33	28	
Newly diagnosed	32	35	
Previous disease	18	15	
csDMARDs therapy (n)			
Sulfasalazine + MTX	5	3	0.715
Hydroxychloroquine + MTX	4	6	0.740
Leflunomide + MTX	5	4	0.999
Methotrexate alone	4	2	0.677

Notes: Data was presented as mean ±SD, median, numbers, interquartile range, and numbers, Control group, rheumatoid arthritis patients treated with methotrexate and placebo, Paroxetine group, rheumatoid arthritis patients treated with methotrexate plus paroxetine, Significance at ($p < 0.05$).

Abbreviations: M, Male; F, Female; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Sr Cr, Hgb, hemoglobin, WBCs, white blood cells, RBCs, red blood cells, serum creatinine; RF, rheumatoid factor, DMARDs, conventional synthetic disease modifying anti-rhematic drugs; MTX, methotrexate.

Regarding disease activity, 34% of patients in the control group had mild disease compared with 44% in the paroxetine group ($p = 0.305$). Concomitant use of other csDMARDs (sulfasalazine, hydroxychloroquine, leflunomide, and methotrexate) was balanced across both groups ($p > 0.05$ for all comparisons).

Effect of Study Medications on DAS-28 CRP

During the follow-up period, 8 patients were lost to follow-up in the control (placebo) group: 5 patients withdrew their consents and we lost contacts for the other 3 patients. 10 patients in the paroxetine group: 5 patients withdrew due to non-compliance, 2 patients withdrew their consents, 3 patients withdrew due to other reasons as shown in Figure 1. To

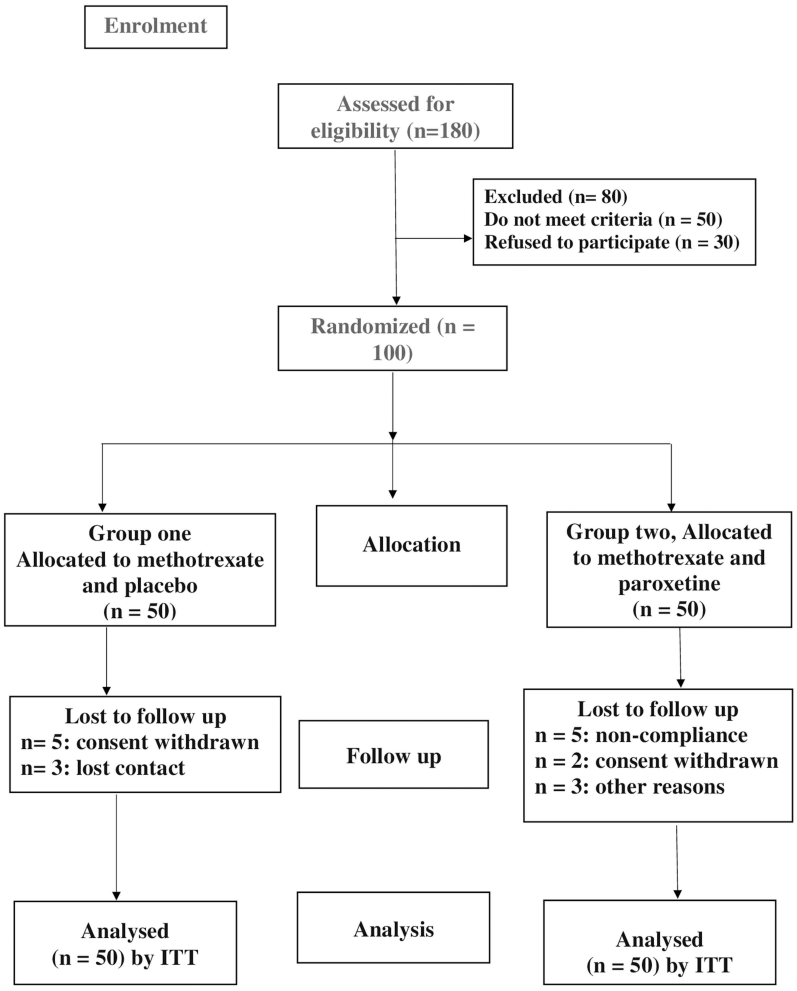

Figure 1 CONSORT diagram showing the flow of participants during the study.
Abbreviation: ITT, Intension to Treat.

preserve the integrity of randomization and reduce bias, an ITT analysis was performed using the BOCF method for handling missing data. All randomized patients were included in the final analysis.

At baseline, there were no significant differences between the control and paroxetine groups in tender joint count (TJC), swollen joint count (SJC), C-reactive protein (CRP), visual analogue scale (VAS), or DAS-28 CRP ($p > 0.05$ for all) as shown in Table 2.

After 3 months of treatment, both groups demonstrated significant improvements from baseline in TJC, SJC, VAS, and DAS-28 CRP ($p < 0.05$ within groups, Wilcoxon test). However, the degree of improvement was more pronounced in the paroxetine group compared with the control group.

Specifically, the median TJC decreased from 7.5 (3–11) to 3 (1.75–6) in the paroxetine group versus 6.5 (4–10) to 5 (2–7) in the control group ($p = 0.006$ between groups, Mann–Whitney test). Similarly, the SJC decreased more markedly in the paroxetine group [5 (2–8.25) to 2 (1–4.25)] compared to the control group [6 (2–8) to 4 (2–6); $p = 0.016$ between groups].

Regarding inflammatory markers, CRP remained essentially unchanged in the control group (10.60 → 9.7 mg/L, $p = 0.933$) but showed a significant reduction in the paroxetine group (10.65 → 7.4 mg/L, $p < 0.0001$). The between-group comparison confirmed a highly significant difference ($p = 0.0006$).

Patient-reported outcomes improved in both groups, with a greater reduction in VAS scores in the paroxetine group [39.5 (30–50) → 20 (12–25)] compared to the control group [41.5 (29–56.5) → 24 (15–36.25); $p = 0.03$ between groups].

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Table 2 Effect of Study Medications on DAS-28 CRP

Character	Control Group (n=50)	Paroxetine Group (n=50)	*p* value
Baseline TJC	6.5 (4–10)	7.5 (3–11)	0.908
After 3 months	5 (2–7)	3 (1.75–6)	0.006**
P-value	0.010*	0.0005*	
Baseline SJC	6 (2–8)	5 (2–8.25)	0.757
After 3 months	4 (2–6)	2 (1–4.25)	0.016**
P-value	0.005*	<0.0001*	
Baseline CRP	10.60 (8.4–14.25)	10.65 (8–13.65)	0.822
After 3 months	9.7 (7.77–15.73)	7.4 (6.25–9.65)	0.0006**
P-value	0.933	<0.0001*	
Baseline VAS	41.50 (29–56.5)	39.50 (30–50)	0.644
After 3 months	24 (15–36.25)	20 (12–25)	0.03**
P-value	<0.0001*	<0.0001**	
Baseline DAS-28	4.586 (4.19–4.84)	4.521 (3.89–4.91)	0.877
After 3 months	3.921 (3.62–4.20)	3.45 (3.21–3.72)	0.005**
P-value	<0.0001*	<0.0001*	

Notes: Data was presented as median, interquartile range, mean, and standard deviation. Control group, rheumatoid arthritis patients treated with methotrexate and placebo, Paroxetine group, rheumatoid arthritis patients treated with methotrexate plus paroxetine. (*) level of significance within the same group using Wilcoxon test. (**) level of significance between groups using Mann Whitney test. Significance at ($p < 0.05$).

Abbreviations: TJC, Tender joint count, SJC, Swollen joint count, CRP, C-reactive protein, VAS, visual analogue scale, DAS-28, disease activity score using 28 joint counts.

Finally, overall disease activity measured by DAS-28 CRP decreased significantly in both groups. The reduction was greater in the paroxetine group [4.521 (3.89–4.91) → 3.45 (3.21–3.72)] than in the control group [4.586 (4.19–4.84) → 3.921 (3.62–4.20); $p = 0.005$ between groups].

Effect of Study Medications on Multidimensional Health Assessment Questionnaire

At baseline, there were no significant differences between the control and paroxetine groups in MDHAQ subscales, including MS, pain score, fatigue score, and PF ($p > 0.05$ for all) as illustrated in Table 3.

After 3 months of treatment, both groups demonstrated significant within-group improvements across most MDHAQ domains ($p < 0.05$, Wilcoxon test). However, the degree of improvement was more pronounced in the paroxetine group compared with the control group in morning stiffness, pain, and fatigue.

Median MS decreased from 92 (75–101.8) to 60 (45.75–88.5) in the paroxetine group versus 89.5 (71.5–100) to 72.5 (59.5–97.5) in the control group, with a significant between-group difference ($p = 0.024$, Mann–Whitney test). Similarly, the pain score decreased to a greater extent in the paroxetine group [7.75 (7.07–8.6) → 4.4 (3.2–7.22)] compared with the control group [7.80 (7–8.52) → 6.35 (4–8.4); $p = 0.03$ between groups].

Fatigue scores improved significantly in both groups, but the reduction was larger in the paroxetine group [7.75 (6.9–8.52) → 4.5 (3.27–7.27)] compared to the control group [7.55 (7–8.4) → 5.85 (4.57–8.25); $p = 0.006$ between groups].

For physical functioning, both groups improved significantly over time (control: $p = 0.0004$; paroxetine: $p = 0.0001$), although the difference between groups at 3 months was statistically non-significance ($p = 0.133$).

Table 3 Effect of Study Medications on Multidimensional Health Assessment Questionnaire

Character	Control Group (n=50)	Paroxetine Group (n=50)	*p* value
Baseline MS	89.50 (71.5–100)	92 (75–101.8)	0.530
After 3 months	72.50 (59.5–97.5)	60 (45.75–88.5)	0.024**
P-value	0.004*	<0.0001*	
Baseline pain score	7.80 (7 −8.52)	7.75 (7.07–8.6)	0.884
After 3 months	6.35 (4–8.4)	4.4 (3.2-0.7.22)	0.03**
P-value	<0.0001*	<0.0001*	
Baseline fatigue score	7.55 (7–8.4)	7.75 (6.9–8.52)	0.696
After 3 months	5.85 (4.57–8.25)	4.5 (3.27–7.27)	0.006**
P-value	0.0002*	<0.0001*	
Baseline PF	7.5 (6.8–8.2)	7.050 (6.47–8.02)	0.208
After 3 months	5 (3.4–8.3)	3.8 (3.32–4.2)	0.133
P-value	0.0004*	0.0001*	

Notes: Data was presented as median, and interquartile range. Control group, rheumatoid arthritis patients treated with methotrexate and placebo, Paroxetine group, rheumatoid arthritis patients treated with methotrexate plus paroxetine. (*) level of significance within the same group using Wilcoxon test. (**) level of significance between groups using Mann Whitney test. Significance at ($p < 0.05$).
Abbreviations: MS, morning stiffness; PF, physical functioning.

Correlation Between Measured Variables in Paroxetine Group

Correlation analysis in the paroxetine group revealed several significant associations between disease activity and patient-reported outcomes. DAS-28 CRP was significantly correlated with morning stiffness ($r = 0.325$, $p = 0.001$), pain score ($r = 0.301$, $p = 0.002$), fatigue ($r = 0.216$, $p = 0.03$), and physical functioning ($r = 0.410$, $p < 0.0001$).

In addition, morning stiffness was significantly correlated with pain ($r = 0.460$, $p < 0.0001$) and fatigue ($r = 0.459$, $p < 0.0001$). A strong correlation was also observed between fatigue and pain ($r = 0.633$, $p < 0.0001$).

Analysis of Drug Related Side Effects Between the Two Study Groups

The incidence of most adverse effects listed in Table 4—including vomiting, nausea, diarrhea, drowsiness, and headache—did not differ significantly between the paroxetine and control groups ($p > 0.05$ for all). In contrast, decreased libido

Table 4 Analysis of Drug Related Side Effects Between the Studied Groups

Side effect	Control Group (n=50)	Paroxetine Group (n=50)	*p* value
Vomiting	3	5	0.715
Nausea	4	7	0.377
Diarrhea	3	7	0.317
Drowsiness	4	8	0.218
Headache	4	6	0.740
Decreased libido	2	11	0.007*

Notes: Data was presented as numbers and percentages, Control group, rheumatoid arthritis patients treated with methotrexate and placebo, Paroxetine group, rheumatoid arthritis patients treated with methotrexate plus paroxetine. (*) significance at ($p < 0.05$) using Chi square test and fisher exact test as appropriate.

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was reported more frequently in the paroxetine group compared with controls (22% vs 4%; p = 0.007). Overall, paroxetine was well tolerated, except for sexual dysfunction, which was observed at a higher rate in patients receiving paroxetine in combination with methotrexate.

Discussion

Although multiple therapeutic options are available for RA, a subset of patients fails to achieve complete remission, indicating the need for effective adjunctive strategies to alleviate pain and residual symptoms. In the present study, adjunctive paroxetine therapy produced a significant reduction in DAS28-CRP compared with the control group after three months of treatment, highlighting its potential role in improving overall disease activity in patients with RA. The DAS28-CRP score reflects a composite index that integrates tender and swollen joint counts, an acute-phase reactant (CRP), and patient-reported global health assessment, thereby providing a robust measure of both inflammatory burden and clinical impact. The observed improvement in DAS28-CRP in the paroxetine group therefore underscores a beneficial effect on both objective markers of inflammation and patient-perceived disease severity. Likewise, in a randomized controlled clinical trial, paroxetine reduced pain and depression associated with RA with fewer adverse effects compared to amitriptyline.[31] Paroxetine also demonstrated high efficacy in improving the clinical manifestations of RA in patients with elevated serum melatonin levels.[32] In addition, paroxetine, in a randomized controlled trial, demonstrated improvement on clinical global impressions (CGI) scale in patients with noncardiac chest pain, indicating general improvement in patient condition.[33] In another randomized controlled trial, paroxetine significantly improved overall fibromyalgia symptomatology, fibromyalgia impact questionnaire, clinical global impression (CGI) scale, and severity scores.[34] Similarly, paroxetine reduced pro-inflammatory cytokines such as TNF-α and IL-6 in arthritis in a mouse model.[35] A case report of 60 year Indian man with RA achieved remission following treatment with a selective serotonin reuptake inhibitor (SSRI), despite lack of response to multiple conventional antirheumatic therapy.[36]

Several mechanisms may explain this improvement. Paroxetine is a SSRI with additional off-target activity as a selective inhibitor of GRK2.[37] GRK2 has been implicated in the pathogenesis of RA by regulating T-cell activation, synovial hyperplasia, fibroblast-like synoviocyte proliferation, and NF-κB–mediated pro-inflammatory signaling.[38] Inhibition of GRK2 by paroxetine has been shown to suppress inflammatory cytokines such as TNF-α, IL-6, and IL-1, while modulating pathways such as PPARγ and RANKL/OPG, which are central to synovial inflammation and joint destruction.[22,35,39] These pleiotropic immunomodulatory effects likely contributed to the reduction in disease activity observed in the current trial. In another mice model, paroxetine exerted immunomodulatory effects in RA by inhibiting GRK2-mediated phosphatidylinositol 3 kinase (PI3K), mammalian target of rapamycin (mTOR), and protein kinase B (AKT) signaling.[20] By translating these preclinical effects into a clinical context, this study provides novel evidence supporting the potential repositioning of paroxetine as an adjunctive therapy in RA.

In our study, patients receiving paroxetine exhibited greater improvements in pain compared to the control group. These findings highlight the broader clinical benefits of paroxetine beyond joint inflammation, addressing dimensions of health that are particularly burdensome to patients with RA. Similarly, patients who suffered from lower back pain and received paroxetine decreased their use of concomitant analgesic medication.[40] However, in a randomized double-blind trial of patients with chronic low back pain, paroxetine did not show significant pain reduction compared with placebo.[41] Paroxetine contributed to pain relief in mice by exerting antinociceptive effects through modulation of opioidergic mechanisms and serotonergic pathways.[42] In addition, paroxetine attenuated both the development and persistence of neuropathic pain in rats by reducing mechanical allodynia and thermal hyperalgesia through inhibition of P2X4 receptor, an adenosine 5′-triphosphate-gated cation channel.[43] It attenuated neuropathic pain in rats through modulating key molecular pathways implicated in chronic pain.[44] In a randomized, double-blind, cross-over study, paroxetine at 40 mg/day significantly alleviated symptoms of diabetic neuropathy, demonstrating comparable efficacy to imipramine but with a superior tolerability and safety profile.[45] In a 6-month prospective trial of patients with painful diabetic neuropathy, paroxetine or citalopram demonstrated better patient compliance, higher treatment satisfaction, and comparable efficacy compared to gabapentin, while also improving mood without negatively impacting quality of life.[46] Thus, paroxetine may provide dual action—dampening peripheral inflammation and modulating central pain mechanisms. However, paroxetine had no influence on fatigue in patients receiving chemotherapy, although it significantly reduced

depressive symptoms compared with placebo. This finding suggests that cancer-related fatigue may not be mediated by reductions in central serotonin (5-HT) levels.[47]

In the present study, patients receiving paroxetine demonstrated greater improvements in MS, and fatigue compared to the control group. MS, a hallmark symptom of RA that reflects ongoing synovial inflammation and cytokine activity, showed a significant reduction in the paroxetine group. This improvement may be linked to the anti-inflammatory effects of paroxetine mediated through inhibition of GRK2 and downstream suppression of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6.[48] Alleviation of morning stiffness has important clinical implications, as it correlates with better functional outcomes and improved quality of life in RA patients.[49] Although physical function improved in the paroxetine group, the difference did not reach statistical significance compared with the control group. Likewise, paroxetine was associated with marginal improvements in quality of life and musculoskeletal function at 12 months in trauma patients.[50] It reduced exercise time to fatigue in individuals with higher aerobic capacity, while no effect was observed in those with lower aerobic capacity.[51] In patients with chronic heart failure, paroxetine significantly reduced depression and improved general health levels, and quality of life compared with placebo.[52] It also demonstrated effectiveness and safety in improving depressive symptoms and health-related quality of life in primary care patients over 9 months.[53] In older adults with depression, maintenance treatment with paroxetine was superior to placebo in preserving health-related quality of life improvements.[54]

Physical functioning, as measured by the MDHAQ, demonstrated improvement in both groups, with a greater magnitude of benefit observed in the paroxetine group; however, the difference did not reach statistical significance. This enhancement may reflect the cumulative effect of reduced joint inflammation, pain relief, and fatigue alleviation, which collectively contribute to improved daily functioning and patient independence. Preservation of physical functioning is critical in RA management, as disability progression is a major determinant of long-term outcomes and healthcare costs. Taken together, these findings suggest that paroxetine exerts a multidimensional therapeutic effect in RA, extending beyond traditional disease activity indices to encompass key patient-reported outcomes. This is particularly relevant in the context of modern RA management, where treatment success is increasingly defined not only by laboratory or imaging measures but also by improvements in quality of life and patient satisfaction.

Although the overall incidence of common adverse effects, including vomiting, nausea, diarrhea, drowsiness, and headache, did not differ significantly between groups, patients receiving paroxetine exhibited a notably higher occurrence of decreased libido. Similarly, paroxetine demonstrated efficacy in alleviating most symptoms of fibromyalgia syndrome, though amitriptyline was generally more effective, with sexual dysfunction being the main side effect of paroxetine.[55] In patients with major depressive disorder, paroxetine was associated with worsening sexual function in men but not in women.[56] Paroxetine caused histological alterations in rat gonads, leading to impaired gametogenesis with decreased spermatogenic cells and ovarian follicles, indicating negative reproductive effects.[57] Analysis of Dutch pharmacovigilance reports (2003–2019) revealed that antidepressants particularly SSRIs were most frequently associated with drug-induced sexual dysfunction, with differing patterns between men and women.[58]

The findings of the current study indicate that disease activity, as measured by DAS-28 score, correlates with key clinical symptoms, including morning stiffness, pain, fatigue, and physical functioning, while morning stiffness significantly interrelated with pain and fatigue. There was also a significant correlation between fatigue and pain. Similarly, DAS28 scores were significantly modulated by patient-reported pain in 557 patients with RA.[59] Clinically significant pain persists in a notable proportion of patients with RA achieving DAS28 remission with pain severity strongly associated with patient-reported global assessment, disability, fatigue, sleep disturbances, and self-efficacy rather than objective measures of inflammation or joint damage.[60] DAS28 with the derived DAS28-P index effectively discriminated patients with RA and coexisting fibromyalgia highlighting the strong influence of patient-reported pain and global health on overall DAS28 scores.[61] Multiple observational studies showed that DAS28 reflects both inflammatory activity and patient-reported outcomes in RA, derived indices such as DAS28-P, tender–swollen difference, and tender to swollen ratio are more strongly associated with non-inflammatory pain mechanisms, including pain sensitization and fibromyalgia, and can predict future pain, highlighting their utility in refining the interpretation of DAS28 as a measure of inflammatory disease activity.[62] Higher DAS-28 scores were significantly associated with impaired basic and instrumental activities of daily living and poorer sleep quality impacting the functional and quality-of-life outcomes in patients

with RA.[63] Fatigue was highly prevalent among patients with RA and demonstrated an independent association with increased disease activity.[64]

A major strength of this study is its randomized, double-blind, parallel-group design, which minimized selection and observer bias, thereby enhancing the validity of the findings. The use of a computer-generated block randomization sequence with allocation concealment ensured balanced treatment assignment. Another strength is the application of an ITT analysis using the BOCF method. This preserved the benefits of randomization, minimized bias from patient dropouts, and allowed all randomized participants to be included in the final analysis, thereby improving the robustness of the results. Furthermore, the study incorporated a comprehensive evaluation of both clinical and patient-reported outcomes. By including DAS28-CRP as the primary endpoint alongside the MDHAQ, the study captured both objective measures of inflammation and subjective patient-centered assessments such as pain, fatigue, and functional capacity.

This study has several limitations that warrant consideration. First, the relatively small sample size and single-center design may limit the generalizability of the findings to broader and more diverse patient populations. Second, the three-month duration of follow-up restricts the ability to draw conclusions regarding the long-term efficacy and safety of adjunctive paroxetine therapy. Third, methotrexate monotherapy was used as the sole comparator, which may not fully reflect contemporary clinical practice where combination csDMARD regimens are commonly employed. Additionally, adverse events were primarily captured through patient self-report without objective monitoring, potentially underestimating or overestimating tolerability. The trial did not incorporate mechanistic or biomarker analyses, limiting insights into the pathways through which paroxetine may exert its clinical benefits. Moreover, NSAIDs, COX-2 inhibitors, and acetaminophen were permitted as needed but not recorded, making the comparison of their use between groups difficult. Furthermore, this study included only patients with mild to moderate rheumatoid arthritis, which may limit the generalizability of the findings. Patients with severe disease were not enrolled because their management typically requires rapid escalation to biologic or targeted csDMARDs, making it ethically inappropriate to delay or randomize them to an investigational adjunctive therapy. Therefore, the observed benefits of paroxetine as an add-on to csDMARDs apply primarily to patients with less advanced disease, and the efficacy and safety of this strategy in severe RA remain unknown and warrant further investigation. Finally, the study population had relatively short disease duration and less than half were seropositive, absence of mental health assessment, the possibility of overlapping with secondary pain mechanisms (eg, central sensitization or early fibromyalgia features) cannot be fully excluded. Although individuals with clinical characteristics suggestive of fibromyalgia were not enrolled, subclinical overlap may have influenced patient-reported outcomes. Future studies should include formal screening tools for fibromyalgia to further clarify this relationship.

Conclusion

This study demonstrated that the addition of paroxetine to csDMARDs in patients with mild and moderate rheumatoid arthritis resulted in significant improvements in disease activity, as measured by DAS-28 CRP, as well as in patient-reported outcomes assessed by the Multidimensional Health Assessment Questionnaire, including morning stiffness, pain, fatigue, and physical functioning. These findings suggest that paroxetine may exert beneficial effects beyond its antidepressant action, potentially contributing to modulation of inflammatory pathways and improvement in overall quality of life. Paroxetine was generally well tolerated, with decreased libido as the primary adverse effect. The relatively small single-center sample, the exclusion of severe RA patients, the short disease duration, the low seropositivity, absence of mental health assessment, the possibility of overlapping with secondary pain mechanisms (eg, central sensitization or early fibromyalgia features) may limit the generalizability of the findings to broader and more diverse patient populations. Further, further large-scale, multicenter trials with longer follow-up periods are warranted to confirm these findings and clarify the underlying mechanisms.

Data Sharing Statement

Data is available upon request from the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or criticallyreviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest.

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