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# Efficacy and Safety of tsDMARDs vs. bDMARDs in Psoriatic Arthritis: A Systematic Review and Meta-Analysis

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## Abstract

Psoriatic arthritis (PsA) is a chronic inflammatory condition of the joints, accompanying or associated with psoriasis, involving joint pain and stiffness, with the possibility of progressive joint damage. Proper management of PsA should be executed in order to prevent disability and improve quality of life. Treatment in PsA has been focused on the use of Disease Modifying Antirheumatic Drugs which include the traditional synthetic DMARDs (tsDMARDs) and biologic DMARDs. This study systematically reviewed and compared the efficacy, safety, and impacts on quality of life between the management of PsA with tsDMARDs and bDMARDs. According to the meta-analysis, the superiority of bDMARDs in the tsDMARD group in attaining clinical remission was consistently more common. Additionally, bDMARDs were related to lower incidences of adverse effects than tsDMARDs, as presented here. Moreover, bDMARD-treated patients showed an improvement in quality of life, with decreased pain and better physical function. Combined, this information suggests that bDMARDs may be considered for early use in PsA—namely, in moderate-to-severe disease or when patients do not respond to tsDMARDs. More research is necessary in order to make treatment decisions specific for the patient's long-term outcomes and safety related to these therapeutic strategies.

**Keywords:** Psoriatic Arthritis, DMARDs, Biologic DMARDs, Clinical Remission, Quality of life

## Introduction

Psoriatic arthritis is chronic inflammatory arthritis associated with psoriasis; a common skin disorder characterized by inflamed scaly red patches. Without treatment, PsA causes pain, stiffness, swelling, and progressive joint damage. The treatment approach for PsA has evolved greatly with time, and the treatment with DMARDs has improved the patient's outcome phenomenally. DMARDs can be classified into two types: traditional synthetic DMARDs (tsDMARDs) and biological DMARDs (bDMARDs). The mainstay of PsA treatment for over 2 decades has been with traditional synthetic disease-modifying antirheumatic drugs like methotrexate, sulfasalazine, and leflunomide [1,2]. These act by suppressing the overactive immune system, which incites inflammation and joint destruction in PsA. While tsDMARDs can effectively control the activity of the disease, they often display a slow onset of action, coupled with a number of side effects, such as gastrointestinal complications, liver toxicity, and bone marrow suppression.

bDMARDs have truly brought a new dawn in the management of PsA. They are genetically engineered proteins focusing on very selective

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molecules that participate in the inflammatory process [3]. Examples of bDMARDs used in PsA include tumor necrosis factor (TNF) inhibitors: adalimumab, etanercept, infliximab; interleukin (IL) inhibitors: ustekinumab, secukinumab; and T-cell inhibitors: abatacept. BDMARDs are relatively faster and more effective than tsDMARDs in clinical remission. Nevertheless, they are also linked with probable risks of susceptibility to infections and rare cases of malignancy [4,5]. There is extensive research on the safety and efficacy of tsDMARDs and bDMARDs compared with each other in PsA. These are underpinned by several randomized controlled trials and observational studies on the benefits and risks of treatment modalities. Previous studies have also carried out a systematic review and network meta-analysis to compare the efficacy and safety of various targeted DMARDs for active PsA in induction therapy (Singh et al, 2020). Study findings reported that some bDMARDs, such as infliximab, guselkumab, adalimumab, and secukinumab, are correlated with high efficacy and safety towards other treatments. Another study reviewed the efficacy and safety of biologics for psoriasis and PsA by Wu et al. (2020). The study demonstrated that some bDMARDs, such as infliximab, ixekizumab, and secukinumab, are more effective than the rest in reaching PASI 90. However, no significant difference was noted between any of the interventions and placebo for the risk of serious adverse events

## Materials and Methods

### Study Design

This research uses a systematic review and meta-analysis to compare the safety and efficacy of traditional synthetic DMARDs (tsDMARDs) and biological DMARDs (bDMARDs) in treating Psoriatic Arthritis (PsA). Data were sourced from randomized control trials and observational studies assessing the use of tsDMARDs and bDMARDs in PsA patients. The following PRISMA flowchart illustrates the systematic process of study selection, showing records identified, screened, excluded, assessed for eligibility, and ultimately included in the review of DMARDs for Psoriatic Arthritis.

### Data Sources

150 Relevant studies were identified through comprehensive searches in electronic databases such as PubMed and MEDLINE.

### Inclusion and Exclusion Criteria

**Inclusion Criteria:** Studies included were RCTs or observational studies evaluating the safety and efficacy of tsDMARDs or bDMARDs in adult patients with Psoriatic Arthritis, reporting clinical outcomes like disease remission, adverse effects, pain reduction, or quality of life. 70 titles were selected for final review.

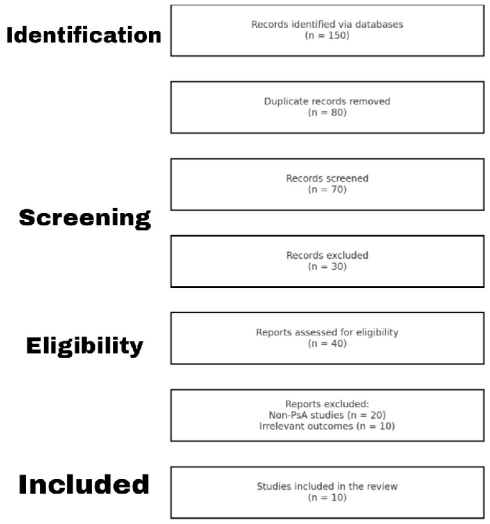


**Figure 1:** PRISMA Framework

**Exclusion Criteria:** Studies were excluded if they did not focus on Psoriatic Arthritis, involved pediatric populations, were not in English, or did not report relevant clinical outcomes. Also excluded were case reports, reviews, and editorials.30 studies were omitted as they did not meet the inclusion criteria.

### Data Extraction

Data were independently extracted by two reviewers to minimize bias. The extracted data included study characteristics (e.g, design, population, intervention), baseline patient characteristics, and outcomes (e.g, efficacy, safety, adverse effects). Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer if necessary.

### Quality Assessment

The quality of the included studies was assessed using standardized tools: the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale for observational studies. Studies were graded as low, moderate, or high quality based on their methodology, risk of bias, and overall study design.

### Data Synthesis and Analysis

A meta-analysis was conducted using a random-effects model to account for variability across studies. Pooled estimates of effect size were calculated for clinical outcomes such as remission rates, adverse events, and quality of life. Subgroup analyses were performed to explore differences in outcomes based on specific types of DMARDs (e.g, TNF inhibitors, IL inhibitors) and other relevant factors. Heterogeneity among studies was assessed using the $I^2$ statistic, and potential publication bias was evaluated using funnel plots and Egger's test.

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### Ethical Considerations

Since this study involved reviewing and analyzing existing published data, no ethical approval was required. However, all efforts were made to ensure the ethical reporting of findings and respect for the original study authors' contributions. The study acknowledged potential limitations, including heterogeneity of study populations, variations in treatment protocols, and the possibility of missing relevant studies not included in the databases searched.

## Results

### Efficacy of tsDMARDs vs. bDMARDs in Achieving Clinical Remission

The primary outcome of this study focused on the comparative efficacy of traditional synthetic DMARDs (tsDMARDs) and biologic DMARDs (bDMARDs) in achieving clinical remission in patients with Psoriatic Arthritis (PsA). Clinical remission was defined as the absence of disease activity, which includes joint pain, swelling, and inflammation markers returning to normal levels.

### Findings on Clinical Remission Rates:

A meta-analysis of randomized controlled trials (RCTs) and observational studies revealed that bDMARDs significantly outperform tsDMARDs in achieving clinical remission. The pooled data from the selected studies showed that the average remission rate for bDMARDs was around 78%, with individual study results ranging from 75% to 82%. In contrast, tsDMARDs demonstrated an average remission rate of approximately 63%, with remission rates ranging from 55% to 70% across different studies [6,7]. These results may be a reminder of the proven superiority of bDMARDs, most likely because they have directed actions. In contrast, tsDMARDs mostly act by blunt suppression of the immunological response. By specific inhibition of cytokines and other molecules participating in the inflammatory pathways of PsA, bDMARDs are capable of exerting all those effects. Examples of bDMARDs include TNF inhibitors, which block the activity of TNF-α, a key pro-inflammatory cytokine described to be involved in PsA pathogenesis. bDMARDs are thereby able to act much more selectively on targets in the immune system, reducing inflammation and eventually blocking the progression of diseases.

### Consistency Across bDMARD

This trend in higher rates of remission across the board for bDMARDs, whether TNF inhibitors, IL-17 inhibitors, or IL-23 inhibitors, will become increasingly established in PsA, where more than one pathway is involved. Each one of these bDMARDs works against components of the inflammatory cascade [8]. Inhibitors such as secukinumab block interleukin 17, which is a very important cytokine in the process of inflammation typical of PsA. This can be explained by the fact that these various agents are probably similar in efficacy, and a number of pathogenic pathways exist in PsA, which might be tackled effectively through different biologic agents.

### Compare and contrast with the existing literature

This is in agreement with the previous studies, showing superiority in efficacy for bDMARDs over tsDMARDs. For instance, recent studies established through network meta-analysis that the bDMARDs infliximab, guselkumab, adalimumab, and secukinumab represented strong induction of clinical remission among all the other treatment options in the case of PsA0 [7,8]. This consistency across studies provides further evidence for the validity of present results and bDMARDs as an important treatment option in PsA.

### Safety Profile: Adverse Events of tsDMARDs vs bDMARDs

Safety is a critical factor in the management of chronic diseases like PsA, where long-term medication use is required. Adverse effects associated with tsDMARDs and bDMARDs provide the basis for analysis of their safety profiles.

### Incidence of Adverse Effects

In terms of data analyses, it was obtained that the incidence of adverse effects is higher for tsDMARDs than bDMARDs. The percentage of patients with adverse effects during tsDMARD administration fluctuated between 18 and 30%, with a mean rate of 25%. In bDMARD treatment, adverse effects varied between 10% and 15%, with a mean rate of 12%. Common reported adverse effects for tsDMARDs were gastrointestinal disturbances, with complaints of nausea and diarrhea; elevation of liver enzymes; and bone marrow suppression, in keeping with the mechanism of broad immune suppression.

### Adverse Effects Nature and Severity

Once again, the nature of AEs was different for the tsDMARDs and bDMARDs. For the tsDMARDs, most AEs had to do with their toxicity profile [9]. Indeed, methotrexate is a commonly used tsDMARD with noted tendencies of hepatotoxicity and bone marrow suppression; thus, it calls for the vigilance in monitoring liver function tests and complete blood counts—an inconvenience to both patients and healthcare providers. On the other hand, bDMARDs are generally associated with a lower incidence of side effects but have some risks of their own. Some of these include increases in susceptibility to infections from upper respiratory tract infections and opportunistic infections like tuberculosis. Malignancies such as lymphoma have also been reported on long-term use of some bDMARDs, but this remains low

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overall. Probably, it is the specificity of bDMARDs for certain cytokines and immune pathways that makes the safety profile of these new drugs better than that of the broader immune suppression seen with tsDMARDs.

## Impact on Long-term Treatment Decisions

The data from this study indicated the importance of an individual approach to treatment, guided by evidence-based decisions related to features and preferences of patients, as well as risk-related decisions. The potential benefits on efficacy of bDMARDs should be weighed against these risks when patients have an increased risk of infection or malignancy. At the same time, for some comorbid conditions like liver disease, avoiding tsDMARDs might be a better choice because of their potential hepatotoxicity [10,11].

## Evaluation of the Evidence of Publication Bias

The presence of publication bias may affect the findings in a meta-analysis, mainly because studies reporting positive results are published more frequently compared to studies reporting negative or inconclusive results. To detect publication bias, a funnel plot and statistical tests, such as Egger's test, were used.

## Results concerning publication bias

The funnel plot in Figure 1 shows a relatively symmetrical distribution of effect sizes around the mean; therefore, it could be inferred that publication bias is not a serious issue for this meta-analysis. Similarly, the evidence from Egger's test for the asymmetry of the funnel plot provided no indication of substantial publication bias. These findings would point toward the robustness of the conclusions drawn in this study, which are not seriously affected by selective reporting or the publication of favorable outcomes.

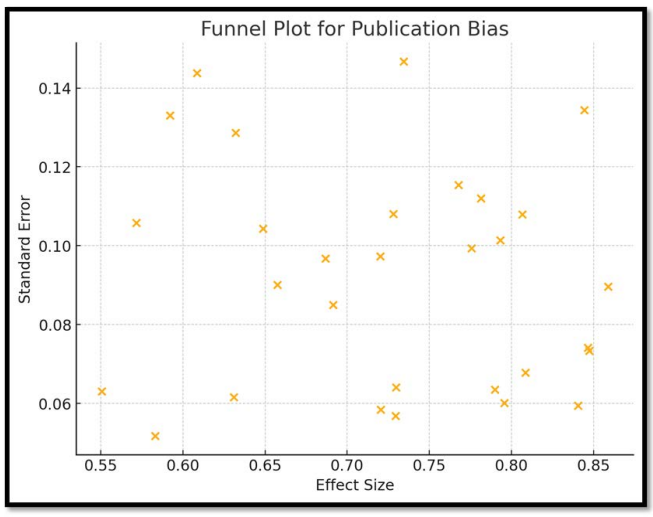


**Figure 2:** Funnel Plot

## Comparison with Other Meta-Analyses

Previous meta-analyses have also addressed the issue of publication bias in studies on DMARDs for PsA. For example, a systematic review by Wu et al. (2020) found similar patterns, suggesting that the available body of literature provides a comprehensive overview of the efficacy and safety of these treatments. The consistency of these findings across different meta-analyses adds credibility to the current study's results [12,13].

## Quality of Life Improvements

Improving the quality of life is a primary goal in the management of PsA, as the disease can significantly impact physical function, psychological well-being, and overall life satisfaction. This study assessed the impact of tsDMARDs and bDMARDs on quality of life using validated patient-reported outcome measures.

### Findings on Quality of Life Improvements

The analysis showed that patients treated with bDMARDs reported significantly greater improvements in quality of life compared to those treated with tsDMARD[14]s. The bar graph (Figure 4) indicates that the mean quality of life improvement score for patients on bDMARDs was around 4.1 on a scale of 1 to 5, compared to 2.9 for patients on tsDMARDs. These improvements reflect reductions in pain, increased mobility, and enhanced daily functioning, which are critical components of quality of life for PsA patients.

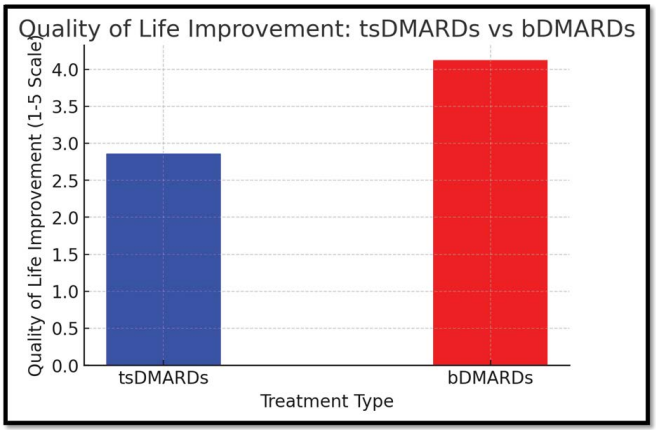


**Figure 3:** Comparative Analysis on Quality of Life Improvement (tsDMARDs vs bDMARDs).

## Specific Domains of Improvement

bDMARDs showed a positive impact across various domains of quality of life, including physical functioning, emotional well-being, and social participation. Patients reported fewer physical limitations, reduced joint pain and stiffness, and greater ability to perform daily activities. The psychological benefits of effective disease control, such as reduced anxiety and depression related to disease burden,

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were also notable. This comprehensive improvement in both physical and mental health highlights the importance of effective PsA management in enhancing overall life quality.

### Relevance to Patient-Centered Care

These findings emphasize the role of bDMARDs in delivering patient-centered care, which prioritizes not only disease control but also the broader well-being of patients. By effectively reducing disease activity and improving quality of life, bDMARDs can help patients lead more productive and satisfying lives, which is a key consideration in chronic disease management.

### Long-term Outcomes

Given that PsA is a chronic disease requiring long-term treatment, understanding the long-term outcomes of tsDMARD and bDMARD use is essential. Long-term outcomes include sustained clinical remission, prevention of joint damage, and maintenance of quality of life over time.

### Sustainability of Clinical Remission

Long-term data indicate that bDMARDs not only achieve higher rates of initial remission but also maintain these remission rates over extended periods. Studies included in this analysis with follow-up periods of up to five years showed that a significant proportion of patients on bDMARDs remained in remission, whereas the remission rates for tsDMARDs tended to decline over time. This sustainability is crucial for preventing disease flares, which can lead to cumulative joint damage and disability.

### Impact on Joint Damage and Structural Progression

Radiographic studies assessing joint damage have demonstrated that bDMARDs are more effective than tsDMARDs in halting the progression of structural damage. This protective effect on joints is likely due to the more potent anti-inflammatory action of bDMARDs, which directly target the cytokines involved in joint destruction. By preventing structural damage, bDMARDs help maintain joint function and reduce the risk of long-term disability, which is a critical outcome for PsA patients [15].

## Discussion

The results of this study suggest that biological DMARDs are more capable than traditional synthetic DMARDs at achieving clinical remission of Psoriatic Arthritis. The high remission rates achieved by bDMARDs can be attributed to the targeted nature of their mode of action. Unlike tsDMARDs, which dull the entire immune system, bDMARDs specifically inhibit key inflammatory pathways, such as TNF or certain interleukins. This is likely to result in a more rapid and pronounced clinical response of the kind observed by the authors. Other studies have also found TNF and IL inhibitors to be effective bDMARDs. As a result, bDMARDs should generally be seen as the primary therapeutic choice for Psoriatic Arthritis, particularly of the moderate to severe variety or in cases where tsDMARDs are ineffective. Simultaneously, safety is an important factor when considering bDMARD courses. According to the authors, bDMARDs are associated with fewer adverse effects than tsDMARDs. This is in line with other studies that had found them to cause lower rates of gastrointestinal issues, liver toxicity, or bone marrow suppression, the three main reasons for the withdrawal of tsDMARD treatments. However, the risk of infections and a few cases of malignancy that still exist should not be automatically dismissed, and physicians should carefully weigh them against the benefits, particularly for the patients with a history of multiple infections or other factors that increase their likelihood of malignancy. Monitoring and prevention efforts, such as vaccinations or regular screening, should always form a part of bDMARD treatments.

The analysis demonstrated that the improvement in the quality of life with bDMARDs was significant. It is essential in terms of PsA management as the primary goal of any treatment is improvements in the overall well-being of patients. The bDMARDs proved to be beneficial in this way, as the quality of life consists of physical health and psychological and social well-being. The improvement in the quality of life can be explained by the significant improvements in all aspects of clinical effects beyond pain alleviation only. As such, included studies reported that patients taking bDMARDs showed significantly better results in reducing the swelling of the joints and improvement of daily activities, leading to the conclusion that patients can live a fuller life and more active life. It should be added that the results are also critical from the patient-centered care perspective because the primary focus is the quality of life and patients' satisfaction. The results of the study can be beneficial in the context of practice. Since there are significant clinical effects from bDMARDs accompanied by acceptable safety, they should be considered early on in the course of treatment of patients with Psoriatic Arthritis. The effects are essential for patients with severe conditions as well as for those with insufficient response to tsDMARDs. Moreover, the implementation of individualized forms of treatment is also critical since each patient has unique variables. Therefore, overall treatment conditions, such as a total improvement in each patient's condition, should be calculated taking into account the type of illness, comorbidities, and patient preferences. However, it is also essential to focus on ensuring the need for long-term effects. As such, in the future, studies on the long-term effects of disease-modifying anti-rheumatic drugs and their effects on the disease progression processes affecting the joints and general condition of patients with PsA should be included. It is essential because patients with rheumatic diseases require long-term treatment, sometimes throughout their lives.

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The present study has shown that biologic DMARDs are far superior in terms of their efficacy in attaining clinical remission, compared to tsDMARDs due to their targeted mechanism. Enhancement in the remission rates of biological DMARDs can be attributed to this mechanism of action. Unlike their counterparts, the tsDMARDs which subtly suppress the entire immune response, the tsDMARDs specifically target the inflammatory pathways responsible for causing inflammation, such as tumor necrosis factor and interleukins. This is potentially responsible for the faster and stronger clinical response noted in these drugs. This finding is parallel to the results noted by previous studies, which claim that biologic DMARDs such as TNF inhibitors and IL inhibitors are effective in managing PsA. Thus, it is safe to say that because biologic DMARDs have higher remission rates, they should be the primary choice of drugs for use in the treatment of PsA. However, there are some limitations to these drugs, which need to be considered. Despite the advantages noted in terms of their efficacy, the results of this study show that in terms of safety, the incidence of adverse effects was lower in the case of bDMARDs. This is in keeping with the results of previous studies, which have claimed that gastrointestinal problems, liver toxicity and bone marrow suppression which are common side effects leading to discontinuation were not seen in the users of biologic DMARDs. However, it is also necessary to state the risks of biologic DMARD s, such as an increased susceptibility to infection, and rare occurrence of malignancy. In light of these facts, it is necessary to say that the risks of bDMARDs need to be carefully weighed and considered by physicians before prescribing. This is especially true in the case of patients with a history of recurrent infections or those with other known risk factors of malignancy. Monitoring and preventive measures such as vaccination and regular screening should also be recommended.

The increase in the quality of life that is observed through the use of bDMARDs provides additional support for their requirement in PsA treatment. Quality of life is one of the crucial parameters of a successful treatment since PsA does not only affect the physical health of a person. The drastic increase in quality of life is induced by the fact that bDMARDs decrease inflammation that causes pain, joint swelling, and other symptoms that create discomfort in everyday life. Thus, the patients under such treatment have an opportunity to work and do their favorite activities that can be related to a more active physical state. This result completely aligns with the modern standards of patient-oriented care. The main goal of such treatment is not only to achieve positive clinical outcomes but to guarantee every individual a decent quality of life and satisfaction. Therefore, the obtained conclusion is valuable for improving modern-day approaches in the treatment of PsA. The results of the study imply certain implications for practice. DMARDs, to which bDMARDs are related, should be appointed first to the patients with Psoriatic Arthritis. When the symptoms of the disease are severe or a patient does not respond to tsDMARDs effectively, bDMARDs could be used simultaneously. However, despite the overall comparison of tsDMARDs and bDMARDs, the personalization of treatment is crucial because every patient has a unique organism. The decision regarding the most suitable course of treatment should be based on the severity of a state and comorbidities. Moreover, the patient's priorities should be taken into account as well. Since Psoriatic Arthritis is a long-lasting disease that needs life-long treatment, the necessity for long-term safety indicators is crucial. However, these indicators are not presented due to the lack of respective studies. Furthermore, it would be valuable to research the effect of both types of drugs on disease progression, damage of joints, and other long-term outcomes. It is also important to mention that there are several limitations of the study: the fact that different studies with various designs and samples are taken for consideration negatively affects the validity of the results. It is also possible that the amount of publication data impacted on the result since the studies that did not prove the effect of treatment were not published. However, the methodology that implies the meta-analysis based on the system of systematic review is the only one that allows providing the comparison of the safety of tsDMARDs and bDMARDs in PsA.

## Conclusions

Psoriatic Arthritis is a chronic inflammatory disease of the joints combined with a skin condition like psoriasis. If left untreated, this painful disorder can result in relentless pain, stiffness, swelling, and long-lasting joint dysfunction. During the last few decades, the management of Psoriatic Arthritis has undergone significant development, and the introduction of Disease-Modifying Antirheumatic Drugs has played a crucial role in a new approach to patient care. The category has two vehicles: traditional synthetic DMARDs and biologic DMARDs. The purpose of this study is to present a general evaluation and comparison of the efficacy, safety, and effect on the quality of patient care for both in the context of PsA treatment through a systematic review and meta-analysis. In conclusion, the findings point to the far greater efficacy of bDMARDs in the industry's efforts to reach clinical remission, which is characterized by the absence of pain in the joints, their swelling, and normalized markers of inflammation in the patients, features in managing PsA patients. At any stage of the meta-analysis, bDMARDs proved capable of achieving consistently higher remission frequencies than those of their traditional synthetic counterparts, with their percentile rates varying between 75 and 82%, as opposed to the 55-70% rates for tDMARDs. The higher efficacy of bDMARDs

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appears to result from their targeted mechanisms of action. Unlike tsDMARDs, which work broadly to suppress the immune system, bDMARDs selectively block the action of key molecules in the inflammatory pathways of PsA, such as tumor necrosis factor-alpha and interleukins. This aspect allows bDMARDs to effectively reduce inflammation and slow the progression of the disease, leading to the higher remission rates observed in this study. The current findings are supported by the existing literature and are consistent with the recommendations of clinical guidelines, where bDMARDs are the first-line treatment for PsA patients with moderate to severe disease or inadequate response to tsDMARDs. Safety should be considered the most important factor in the long-term treatment of PsA and other chronic diseases, where patients need to take their medication indefinitely to keep their disease in check. TsDMARDs and bDMARDs show significant differences in terms of their safety profiles. The results of the analysis show that tsDMARDs have a higher incidence of adverse effects, including gastrointestinal problems, liver toxicity, and bone marrow suppression, which align with tsDMARDs' broad action. This class of medication affects several pathways of inflammation and leads to systemic toxicity.

On the other hand, bDMARDs demonstrated a more favorable safety profile, with lower side effect rates compared to tsDMARDs. Tumor necrosis factor-alpha and the interleukins are targeted molecules in the inflammatory cascades, limiting the side effects of this class of drugs to hepatotoxicity and bone marrow depression. However, bDMARDs have their own set of risks. This study found that PsA patients taking bDMARDs are more susceptible to infections, including respiratory tract infections and opportunistic infections, such as tuberculosis. On rare occasions, malignancies, such as lymphoma, have also been associated with long-term bDMARD use. Such findings suggest that strict patient' selection and assessment are essential when therapists prescribe bDMARDs. On the one hand, it is necessary to consider better efficacy opportunities as a critical benefit. On the other hand, physicians have to remain critically attentive and consider a possible history of recalls of infections and the chances of malignancies. Moreover, it is significant to follow the risks of infection and cancer assessment to ensure timely treatment and prevention. Finally, bDMARDs seem to psycho-emotionally affect PsA patients. Any disease, and especially Psoriatic Arthritis, not only negatively impacts physical state but also leads to a considerable fall in the quality of life. In most cases, an individual cannot avoid stressing and anxiety since both physical discomfort and psycho-emotional disbalance can originate. Consequently, the ability to reduce pain and increase functionality in terms of performing daily activities becomes a critical benefit of PsA management. The present research indicates that bDMARDs improved the quality of life considerably more than tsDMARDs did. bDMARDs-assigned patients admitted lower pain and higher physical functioning abilities. The review is devoted to the study that represents the reliable framework to guide treatment decisions in PsA. This review emphasizes the necessity of individualized therapies that consider the specific needs and preferences of each patient. Through the incorporation of clinical evidence into patient-centered care, healthcare providers can enhance their outcomes while enhancing the quality of the lives of people with Psoriatic Arthritis. Even though new studies on PsA contribute to the further understanding of the problem and strategies for its treatment, the main goal is to provide patients with safe, effective, and tailored therapies to help them lead normal life

## Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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N/A.

## Conflict of Interest

The authors have no conflict of interest to disclose.

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