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REVIEW

Association Between Janus Kinase Inhibitors Therapy and Mental Health Outcome in Rheumatoid Arthritis: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) is a chronic debilitating illness, usually associated with mental health ailments. Literature reports contradictory observations about the association between recent RA pharmacotherapies and mental health. We systematically reviewed RA randomized control trials to synthesize the association between Janus kinases (JAK) inhibitors therapy and mental health.

Methods: We systematically searched clinical trials of JAK inhibitor intervention reporting mental health outcomes using short form-36 (SF-36) in PubMed, Embase, and Scopus databases from inception to February 2021. We have selected the studies and extracted the data, adhering to Preferred Reporting Items of Systematic reviews and Meta-Analysis (PRISMA) guidelines. We have pooled the mean change of SF-36 mental component score (MCS) between JAK inhibitors and comparator therapy with a 95% confidence interval.

Results: Of the 2915 searched studies for systematic review, 19 studies involving 14,323 individuals were included for the meta-analysis. The pooled mean reduction in SF-36 MCS scores (after minus before) with JAK inhibitors was 4.95 (4.41–5.48). The pooled mean difference of incremental mean change in SF-36 MCS score between JAK monotherapy and comparator was 1.53 (0.88–2.18). The improvement in SF-36 MCS scores with JAK inhibitor therapy is greater than the minimum clinically important difference (MCID) value of 2.5. However, on separate analysis with comparator drugs like methotrexate and standard treatment, the MCS scores did not exceeded the MCID value and were also not statistically significant.

Conclusions: JAK inhibitors results in clinically meaningful improvement in the mental health scores of the RA patients.

PROSPERO Registration ID: 2021 CRD42021234466.

Keywords: Rheumatoid arthritis; Janus kinase inhibitors; Tofacitinib; Baricitinib; Upadacitinib; Filgotinib; Mental health; Short form-36

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Highlights

What is already known about this subject?

From individual trials, each JAK inhibitor, separately had an impact on the mental health in patients with rheumatoid arthritis, but the synthesized result was limited.

What are the new findings?

From our study, the pooled results of JAK monotherapy was found to have a clinically meaningful improvement in mental health compared to baseline/pre-treatment mental health.

The pooled results of JAK inhibitors + methotrexate was found to be effective than disease-modifying antirheumatic drugs in improving the mental health of RA patients.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease prevalent in 0.5–1.0% of individuals, which affects joints [1]. Functional ability is highly compromised in RA patients, causing a substantial impact on both physical and mental quality of life. Literature suggests that about 17% of RA patients suffer from depression, and 25.1% show signs of anxiety [2]. Poor mental health is linked to various detrimental outcomes in RA, including an increased risk of death [3], severe disease activity [4], impaired physical function, increased pain [5], work inability, and fatigue [6]. According to a 2013 systematic review, the pooled depression estimates derived from gold-standard clinical interviews indicate that severe depression affects 16.8% of RA patients [7]. Therefore, mental health is an important component of clinical trial assessment in RA.

Patient-reported outcomes such as short form-36 (SF-36), EuroQoL's five dimensional questionnaire [EQ-5D], Health Assessment Questionnaire are often used to assess the health status of individuals and to study the effect of RA treatments in clinical trials [8]. SF-36 is a validated health-related quality of life (HRQOL) instrument used in a broad spectrum of medical conditions to measure the patient's physical and mental health status as well as the quality of life (QoL) [9]. According to recent research, RA treatment may help RA patients with high levels of inflammation improve their mental health [10]. This could be associated with increased levels of inflammatory markers in depressed individuals [11]. Therefore, it is speculated that targeting inflammatory molecules could be beneficial in improving mental health symptoms. In the last two decades, RA treatment has evolved with newer biologic and targeted therapies which specifically inhibit the inflammatory cytokines [tumor necrosis factor (TNF-α), interleukin-6 (IL-6)], and small molecules [Janus kinase (JAK)] respectively [12]. Existing evidence suggests that TNF-α and IL-6 inhibitors reduce depression/improves mental health in people with chronic physical illness [13, 14]. It is also observed that antidepressants that regulate the JAK pathway may be beneficial in decreasing RA peripheral inflammation, according to preliminary findings [15–17]. Therefore, JAK inhibitors might have the potential to mitigate the depression observed in RA patients thereby improving their mental health. Several RA clinical trials with JAK inhibitors have reported patient-reported outcomes (particularly SF-36) [18–35] however were inconclusive about its benefit on mental health. Therefore, we aimed to determine the effect of JAK inhibitors on the mental health of RA patients by systematic review and meta-analysis of SF-36 mental component score (MCS).

METHODS

We conducted a systematic review and meta-analysis adhering to the guidelines of PRISMA [36], and the protocol was registered in PROSPERO (Prospero 2021 ID: CRD42021234466). This article is based on previously conducted studies and does not contain any new studies

with human participants or animals performed by any of the authors.

Screening and Study Selection

Clinical trials of JAK inhibitors reporting the mental health of RA patients assessed using SF-36 were systematically searched in PubMed, Embase, and Scopus using search terms from inception until February 2021. The PIOS approach, i.e., population (RA), intervention (JAK inhibitors-tofacitinib, baricitinib, upadacitinib, filgotinib and peficitinib), outcome (SF-36), and study design (clinical trial) was employed to construct the search terms. The details of the search strategy are provided in Supplementary Tables 1, 2, and 3. In line with the objectives, studies that reported SF-36 MCS scores among adult RA individuals treated with JAK inhibitors were included. Studies involving other arthritis, such as juvenile idiopathic arthritis or psoriatic arthritis, were excluded. Letter to editors, case reports, conference abstracts, observational studies, reviews, in vitro studies/pre-clinical studies was exempted from the review. The titles and abstracts of the studies were independently screened by two reviewers (GS and BSB) using the Rayyan-web app for systematic reviews after removing the duplicates [37]. Later full texts of studies were screened based on selection criteria, and the final list of selected studies was prepared on authors' mutual consensus (GS, BSB, and MK) (Fig. 1).

Data Extraction and Management

From the selected studies, relevant details were extracted using a data extraction form created in Microsoft Excel v.2016. The data extraction form recorded participant details and characteristics, including mean age, gender (%), RA diagnosis criteria, and SF-36 scores. The SF-36 consists of eight domains, including four scales for the physical health measure comprising physical functioning (ten items), role-physical (four items), bodily pain (two items), and general health (five items) and four scales for the mental health measure composed of vitality (four items), social functioning (two items), role-emotional (three items), and mental health (five items) [9]. The sum of all domains with different weights provides two summary scores, a physical component score (PCS) and a mental component score (MCS). Higher scores indicate better health status. We extracted and used the MCS component scores.

Additionally, the data extraction sheet also recorded author names, study title, year of publication, follow-up period, sample size, intervention, comparator, the country where the study was conducted, trial name, and phase of the clinical trial. Data on central tendency (mean/median) and dispersion [standard deviation (SD)/standard error (SE)/interquartile range (IQR)/95% confidence interval (CI)] were extracted from the included studies by GS, verified independently by MH and finalized on mutual consensus(GS, BSB, and MH).

Assessment of Risk of Bias

We assessed the risk of bias (ROB) using a revised Cochrane risk of bias tool for randomized trial (RoB-2 tool) [38]. ROB-2 assesses the ROB in randomized control trials (RCTs) in the five domains, including randomization process, deviation from intended intervention, missing outcome data, measurement of outcome, and selection of reported results. Two authors (MH and MK) independently assessed the quality of included studies, and disagreements were resolved by consensus.

Statistical Analysis

Two approaches were used to determine the effect of JAK inhibitors on mental health. The first approach, the incremental mean change of SF-36 MCS scores, was estimated as the difference between SF-36 MCS scores between baseline and last follow-ups for each of the studies. The incremental mean changes of SF-36 MCS scores were then pooled across all the studies to estimate the change/improvement in mental health scores with the JAK inhibitor treatment. In the second approach, we have calculated the mean difference (MD) between the SF-36 MCS

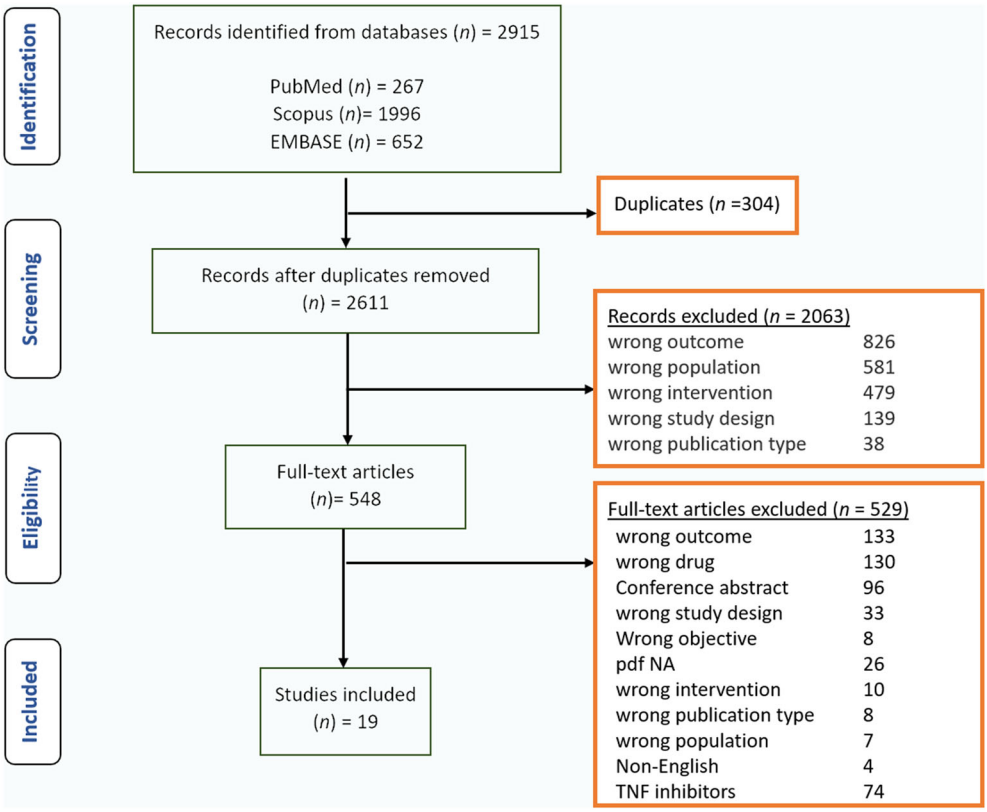

Fig. 1 Prisma flow chart of selection of studies

scores' incremental mean change of JAK inhibitors therapy with that of other DMARDs/placebo. This MD was pooled across all the studies to provide the relative change or improvement with the JAK inhibitors compared to other DMARDs/placebo. In both approaches, the respective effect measures were pooled along with their 95% CI. The random-effects model with the Hedge's method was used if heterogeneity was present; otherwise, a fixed-effect model was employed for pooling.

Heterogeneity was assessed using visual inspection of forest plots, Cochran's Q test, and I^2 statistics. I^2 describes the percentage of the variability in effect estimates due to heterogeneity rather than sampling error (chance); the I^2 value of $\geq$ 40% was considered as presence of substantial heterogeneity [39]. Cochran's Q is the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method. Q is a Chi-square statistic with k (number of studies) minus one degree of freedom. If the $Q(k-1)$ value is greater than the tabulated value (obtained using degrees of freedom) and the p value is < 0.1 then heterogeneity is considered to be present [40].

Subgroup/sensitivity analysis was performed to investigate the influence of follow-up duration, phases of the clinical trial, and comparator drugs on heterogeneity. However, it was conducted only if sufficient (at least ≥ 2) studies were available for each subgroup. The sensitivity analysis was conducted by pooling incremental mean change of SF-36 MCS score for JAK inhibitors and comparator to know individual drug effects on the mental health outcome. Data were recorded using Microsoft Excel v.2016, and analysis was performed using Stata version 16 [41]. All results were considered statistically significant at $p < 0.05$, except for the subgroup analysis and heterogeneity test, wherein $p < 0.10$ was regarded as significant.

Further, the SF-36 MCS scores greater than 2.5 MCID was considered to indicate clinically significant improvement in mental health [42]. Meta-regression was performed with SF-36 PCS to see if improvement in SF-36 MCS is affected by PCS. Publication bias was assessed using a funnel plot (asymmetry) and Egger's test ($p < 0.05$) [43], only if sufficient (at least ten) number of studies were available for pooling. Further, on identifying asymmetry in the funnel plot, the source of asymmetry was explored using a contour-enhanced funnel plot.

RESULTS

Description of Studies

The electronic search retrieved 2915 articles. After removing duplicates and screening titles and abstracts, 548 full texts were screened. Full-text scrutiny resulted in the selection of 19 studies involving 14,323 individuals for the final synthesis [18–35, 44]. The PRISMA flowchart shows the selection of studies (Fig. 1).

The characteristics of these 19 included studies are described in Table 1. The trial participants' mean age was 52.8 years and were predominantly (81.9%) females. The sample size in individual studies ranged from 136 to 1593 participants. The interventions reported were tofacitinib, baricitinib, upadacitinib, and filgotinib either as monotherapy or combination with methotrexate (MTX) in 11, four, three, and one studies, respectively. Because none of the peficitinib studies reported SF-36, it was excluded from this review. The comparator was either placebo, MTX, or placebo plus MTX or adalimumab (TNF-α inhibitor). Fifteen studies were conducted in phase 3, and four studies were conducted in phase 2 of the clinical trial. All the include studies have assessed the efficacy of the JAK inhibitor, except one study, which has assessed the monthly medical expenditure and job loss [44]. Two studies [19, 22] (10.5%) were conducted in European countries, and the United States of America, two studies [26, 27] (10.5%) were conducted in Japan, one study [31] (5%) in China, and the remaining 14 studies (73.6%) were conducted all over the world. In six out of 19 studies [18, 19, 27, 29, 30, 32], American College of Rheumatology (ACR) 1987 criteria were used for RA diagnosis, and in two studies [18, 23] 2010 ACR/EULAR was used. The diagnostic criteria were not stated in other studies. The follow-up duration for these studies ranged from 6 to 284 weeks. ROB assessment showed a low ROB for all the studies included (Supplementary Fig. 1).

Results of Pooling

Pooled incremental mean change in SF-36 MCS score with JAK monotherapy from 17 studies was 4.95 (4.41–5.48, $I^2 = 77.09\%$) with high heterogeneity (Fig. 2). The SF-36 MCS scores greater than 2.5 (MCID) indicate significant improvement in RA patients' mental health following JAK monotherapy. The test of θ, with $p < 0.1$, indicates that pooled results are statistically significant. Funnel plot shows symmetry suggesting no publication bias (Supplementary Fig. 2).

Subgroup analysis based on follow-up durations (< 24 and ≥ 24 weeks) and phases of clinical trials (phase 2 and phase 3) showed similar results (Supplementary Figs. 3, 4). However, high heterogeneity (< 24 weeks, $I^2 = 77.38\%$; ≥ 24 weeks $I^2 = 78.77\%$) was observed in both the subgroups, which could not explain the cause for overall heterogeneity (Supplementary Fig. 3). Similarly, subgroup analysis based on the phases of clinical trials (phase 2 and phase 3) also showed similar results with high heterogeneity (phase 2, $I^2 = 63.78\%$; phase 3, $I^2 = 79.07\%$) in the subgroups (Supplementary Fig. 4). RA patients included in this meta-analysis either had inadequate response to MTX alone, csDMARDs alone, bDMARDs alone or both csDMARDs and bDMARDs. We performed a subgroup analysis to observe if the incremental change in SF-36 MCS differ based on their prior treatment responses and could be contributing to the heterogeneity (Supplementary Fig. 5). Among the subgroups, RA patients who had an inadequate response to MTX alone showed a pooled incremental mean change of 5.19 and the

Table 1 Characteristics of included studies (qualitative synthesis)

Author	Year	Trial name	Country	Sample size	Mean age (years)	Female (%)	Duration (in weeks)	Intervention	Comparator
Coombs et al. [22]	2009	NCT00147498	Belgium, Brazil, Canada, Germany, Italy, Mexico, Spain, USA	264	50.6	85.6	6	Tofacitinib (5 mg, 15 mg, 30 mg BID)	Placebo
Emery et al. [25]	2017	RA-BUILD	Argentina, Australia, Belgium, Canada, Croatia, Czechia, Germany, Hungary, India, Italy, Japan, Korea, Mexico, Russia, Slovakia, Spain, Taiwan, UK, USA	684	51.8	81.9	24	Baricitinib (2 mg, 4 mg) QD + csDMARD	Placebo + csDMARD
Genovese et al. [18]	2018	DARWIN-1 DARWIN-2	Argentina, Australia, Austria, Belgium, Bulgaria, Chile, Colombia, Israel, Latvia, Mexico, Moldova, New Zealand, Poland, Russian Federation, Spain, Ukraine, USA	877	52.75	81.3	24	MTX + filgotinib (50 mg, 100 mg, 200 mg) MTX + filgotinib (25 mg, 50 mg, 100 mg) BID Filgotinib (50 mg, 100 mg, 200 mg) QD	MTX + placebo, placebo
Keystone et al. [24]	2017	RA-BEAM	Argentina, Belgium, Canada, China, Croatia, Czechia, France, Germany, Slovakia, Slovenia, South Africa, Spain, Switzerland, Taiwan, UK, USA	1305	53.3	77.2	52	MTX + baricitinib (2 mg, 4 mg) ID	Placebo + MTX, adalimumab + MTX
Li et al. [31]	2018	ORAL Sync	China	792	52.3	81.4	52	MTX + tofacitinib (5 mg) BID tofacitinib (10 mg) BID	Placebo advanced to intervention at third month

Table 1 continued

Author	Year	Trial name	Country	Sample size	Mean age (years)	Female (%)	Duration (in weeks)	Intervention	Comparator
Rendas-Baum et al. [44]	2017	ORAL-Step ORAL-standard	Australia, Austria, Belgium, Brazil, Canada, France, Italy, Korea, Puerto Rico, Spain, Taiwan, USA	1116	53.95	82.85	24	MTX + tofacitinib (5 mg, 10 mg) BID Tofacitinib (5 mg, 10 mg) BID	Placebo advanced to intervention at third month
Schiff et al. [27]	2017	RA-BEGIN	Argentina, Austria, Belgium, Brazil, Canada, Germany, Greece, India, Italy, Japan, Korea, Mexico, South Africa, Sweden, UK, USA	584	49.9	72.8	52	Baricitinib 4 mg MTX + baricitinib(4 mg)	MTX
Smolen et al. [26]	2016	RA-BEACON	Argentina, Australia, Austria, Belgium, Canada, Denmark, France, Germany, Greece, Israel, Italy, Japan, Korea, Mexico, Netherlands, Poland, Puerto Rico, Spain, Switzerland, Turkey, UK, USA	527	55.7	81.7	24	Baricitinib (2 mg, 4 mg)	Placebo
Strand et al. [32]	2014	NCT00960440	Australia, Austria, Belgium, Brazil, Canada, France, Germany, Ireland, Italy, Korea, Puerto Rico, Spain, Taiwan, USA	399	55	84	24	MTX + tofacitinib (5 mg, 10 mg) BID	Placebo advanced to intervention at third month

Table 1 continued

Author	Year	Trial name	Country	Sample size	Mean age (years)	Female (%)	Duration (in weeks)	Intervention	Comparator
Strand et al. [20]	2015	NCT00814307	Brazil, Bulgaria, Chile, Colombia, Czech Republic, Dominican Republic, Germany, India, Malaysia, Mexico, Philippines, Poland, Puerto Rico, Russian Federation, Ukraine, USA	611	51.8	86.6	24	Tofacitinib (5 mg, 10 mg) BID	Placebo, placebo + tofacitinib (5 mg) BID
Strand et al. [30]	2016	ORAL START TRIAL	Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Czechia, Dominican Republic, Germany, Hungary, India, Korea, Malaysia, Mexico, New Zealand, Sweden, Taiwan, Thailand, Ukraine, USA	956	49.6	79.3	108	Tofacitinib (5 mg, 10 mg) BID	MTX
Strand et al. [23]	2019	ORAL strategy	Argentina, Australia, Bosnia and Herzegovina, Bulgaria, Canada, Chile, Czechia, Estonia, Israel, Korea, Latvia, Lithuania, Mexico, Peru, Philippines,, Spain, Taiwan, Thailand, Turkey, UK, USA	1146	50.1	82.9	52	Tofacitinib 5 mg BID tofacitinib 5 mg BID + MTX	ADA + MTX

Table 1 continued

Author	Year	Trial name	Country	Sample size	Mean age (years)	Female (%)	Duration (in weeks)	Intervention	Comparator
Strand et al. [34]	2019	SELECT-NEXT	Argentina, Australia, Austria, Belgium, Bosnia, Bulgaria, Canada, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russia, Slovakia, South Africa, Spain, Switzerland, Taiwan, Turkey, Ukraine, UK, USA	661	55.7	78.7	12	Upadacitinib (15 mg, 30 mg)	Placebo
Strand et al. [21]	2019	SELECT-BEYOND	Australia, Austria, Belgium, Canada, Czechia, Estonia, Finland, France, Germany, Poland, Portugal, Puerto Rico, Russian Federation, Slovakia, Spain, Sweden, Switzerland, Turkey, UK, USA	498	57.1	83.9	12	Upadacitinib (15 mg, 30 mg)	Placebo
Strand et al. [35]	2020	SELECT-EARLY, SELECT-MONOTHERAPY	Argentina, Australia, Belarus, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Puerto Rico, Romania, Russian Federation, Serbia, Slovakia, Slovenia, South Africa, Spain, Switzerland, Taiwan, Tunisia, Turkey, Ukraine, UK, USA	1593	54	78.2	12	Upadacitinib (15 mg, 30 mg)	Placebo

Table 1 continued

Author	Year	Trial name	Country	Sample size	Mean age (years)	Female (%)	Duration (in weeks)	Intervention	Comparator
Strand et al. [29]	2020	ORAL Scan	Australia, Brazil, Bulgaria, Canada, Colombia, Czech Republic, Greece, India, Japan, Korea, Mexico, Poland, Taiwan, Ukraine, USA	797	52.8	85.2	108	MTX + tofacitinib (5 mg, 10 mg) BID	Placebo advanced to intervention at third month
Tanaka [28]	2011	NCT00603512	Japan	136	51.3	86	12	Tofacitinib (1 mg, 3 mg, 5 mg, 10 mg) BID	Placebo
Wallenstein [19]	2016	CONSORT (Comb) CONSORT (Mono)	Argentina, Brazil, Bulgaria, Chile, Czech Republic, Hungary, Mexico, Poland, Slovakia, Spain, Sweden, Turkey, USA	891	53.3	83.4	24	Tofacitinib (1 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg) QD + MTX Tofacitinib (1 mg, 3 mg, 5 mg, 10 mg, 15 mg) BID	Placebo, adalimumab 40 mg QOW
Yamanaka et al. [33]	2016	A3921041	Japan	486	52.6	83.1	284	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID

QD once a day, *BID* twice a day, *MTX* methotrexate, *SF-36 MCS score* short form-36 mental component summary score, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs

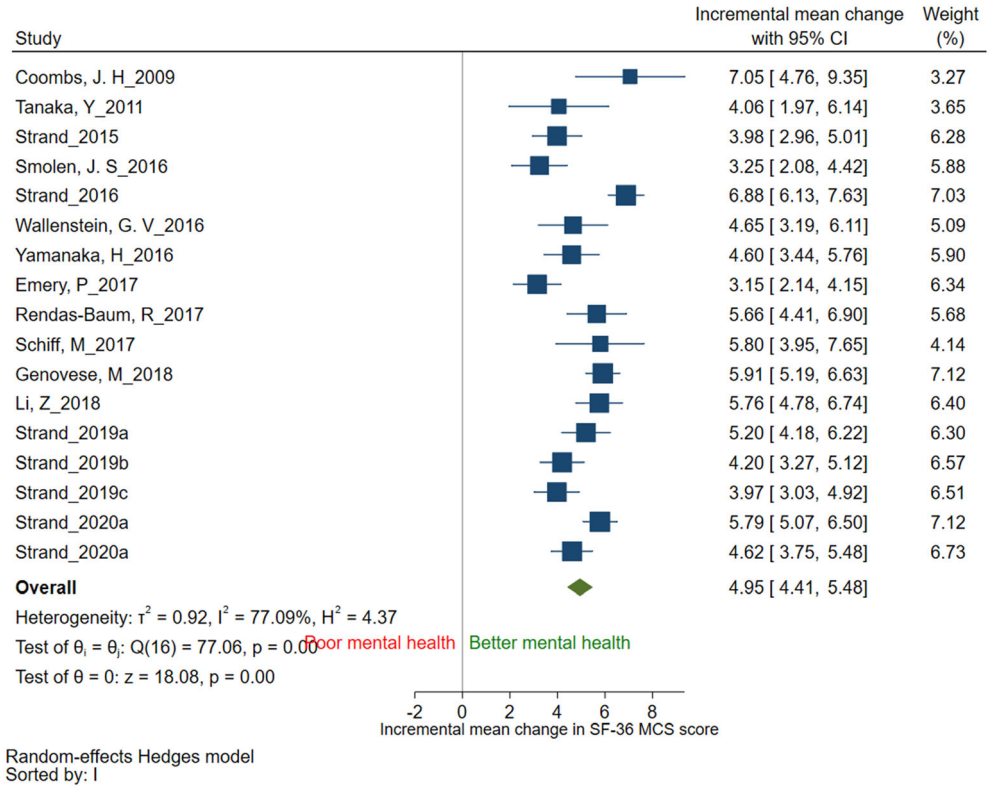

Fig. 2 Forest plot showing the pooled incremental mean change in SF-36 MCS score with JAK monotherapy

heterogeneity decreased to 23.28% in the subgroup. RA patients who showed inadequate response to MTX/TNF-α showed the highest incremental mean change of 7.05 (reported in one study only) followed by 6.27 incremental mean change in treatment naïve patients.

Sensitivity analysis was performed by separately pooling the effect measure for baricitinib, tofacitinib, and upadacitinib to assess the effect of individual JAK inhibitors on mental health (Supplementary Figs. 5, 6, 7). Pooled incremental mean change of SF-36 MCS scores are greater than 2.5 for all the drugs, with highest for tofacitinib [5.32 (4.62–6.03, I^2 = 67.83%)] (Supplementary Fig. 6), followed by upadacitinib [4.68 (3.89–5.47, I^2 = 70.59%)] (Supplementary Fig. 7) and baricitinib [3.93 (2.24–5.62, I^2 = 80.44)] (Supplementary Fig. 8). Only one study involving filgotinib reported mental health outcomes measured using SF-36 in RA patients. Hence separate analysis could not be performed for filgotinib. However, the individual study of filgotinib showed an incremental mean change of 5.4 in the SF-36 MCS, which is greater than the MCID value of 2.5, indicating clinically meaningful improvement in mental health.

Pooled mean difference of incremental mean change in SF-36 MCS score between JAK inhibitors and other therapies was 1.53 (0.88–2.18, I^2 = 24.32%) (Fig. 3). The positive mean difference indicates a statistically significant, greater improvement in SF-36 MCS scores with JAK inhibitors. Sensitivity analysis was performed by separately pooling the effect measure for JAK inhibitors vs. placebo, JAK inhibitors vs. any DMARD and JAK vs. adalimumab to assess the effect of JAK inhibitors in comparison with placebo/other DMARDs. Pooled incremental mean change in SF-36 MCS score for JAK monotherapy vs. placebo was 1.07 (− 0.28–2.43, I^2 = 37.24%) (Supplementary Fig. 9), indicating no statistically significant difference between JAK monotherapy and placebo. Pooled incremental mean change in SF-36 MCS score for JAK monotherapy vs. any

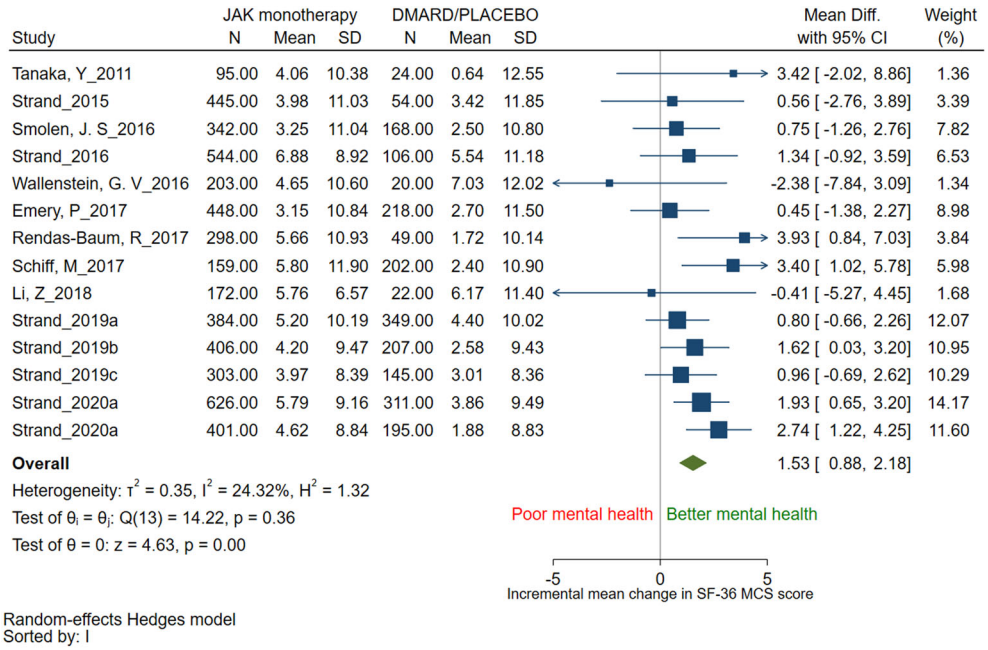

Fig. 3 Forest plot showing the pooled mean difference of incremental mean change in mental health component of short form-36 questionnaire score between JAK inhibitors and other therapies for rheumatoid arthritis

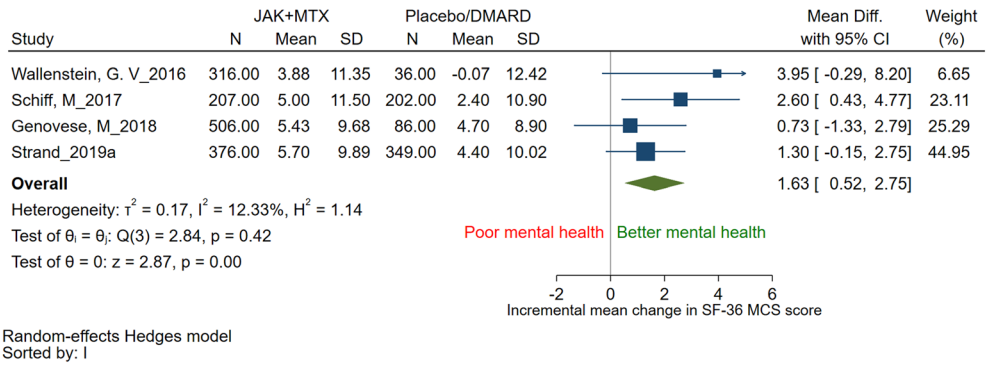

Fig. 4 Forest plot showing the results of pooled mean difference of incremental mean change in mental health component of short form-36 questionnaire score between JAK combination therapy and placebo/DMARDs

DMARD and JAK vs. Adalimumab was 1.72 (0.84–2.59, I^2 = 36.39%) and 1.04 (0.10–1.99, I^2 = 0%) (Supplementary Figs. 10, 11), indicating significantly higher SF-36 MCS scores in patients treated with JAK monotherapy.

Pooled mean difference of incremental mean change in SF-36 MCS score with JAK combination therapy and placebo/DMARDs was obtained from four studies (Fig. 4). Pooled mean difference was 1.63 (0.52–2.75, I^2 = 12.33%), indicating JAK inhibitors + MTX improves the mental health of RA patients better than placebo/DMARD. Publication bias was not assessed due to insufficient studies.

Sensitivity analysis was performed by separately pooling the effect measure for JAK + MTX vs. DMARD (Supplementary Fig. 12). Pooled incremental mean change of SF-36 MCS score was 1.45 (0.41–2.49, I^2 = 0%), showing that JAK inhibitors + MTX are significantly effective than DMARDs in improving the mental health of RA patients. Meta-regression

analysis revealed that an improvement in MCS is associated with improvement in PCS following JAK treatment [coefficient = 0.093, (0.38–0.67), R^2 = 27.4, p = 0.009] (Supplementary Fig. 13a). However, when meta-regression was performed for mean difference between the SF-36 MCS scores' incremental mean change of JAK inhibitors therapy with that of other DMARDs/placebo, we observed that improvement in MCS was independent of PCS change [coefficient = 0.04 (− 0.357–0.438), R^2 = 0, p = 0.84] (Supplementary Fig. 13b).

DISCUSSION

We conducted a systematic review of RCTs to synthesize the effect of JAK inhibitors on the mental health of adult RA patients. With JAK inhibitors monotherapy, we observed a clinically noteworthy improvement in mental health from baseline in RA patients. Furthermore, when compared to other DMARDs/placebo, JAK inhibitors showed better improvement in mental health of RA patients. Among all the JAK inhibitors, tofacitinib showed a greater improvement in mental health followed by upadacitinib and baricitinib.

A 2018 systematic review that focused solely on the impact of biologic and targeted therapies of RA such as TNF-α, IL-6, and JAK inhibitors on mental health outcomes concluded that targeted biologic DMARDs showed similar effectiveness on mental health as conventional DMARDs [14]. However, the observations were not specific to JAK inhibitors. Meta-analysis indicates that JAK inhibitors surpassed conventional synthetic DMARDs and adalimumab in terms of improving mental health in RA patients. JAK inhibitors are effective in RA in part by inhibiting IL-6, a pleiotropic pro-inflammatory cytokine that contributes to synovial inflammation, articular joint destruction, and some of the systemic features seen in RA, according to the literature [45]. However, it is unclear whether improvements in mental health are due to bDMARDs directly influencing the inflammatory pathways or physical health improvements such as pain and disability reduction. When we meta-regressed the incremental mean change in MCS with SF-36 PCS scores in our meta-analysis, we found that improvement in MCS was independent of PCS but not statistically significant. Hence, evidence on whether JAK inhibitors could be beneficial in improving mental health regardless of whether patients respond clinically is inadequate. According to a network meta-analysis that compared the efficacy of tofacitinib, baricitinib, and upadacitinib, upadacitinib 15 mg once daily is the most effective in terms of ACR response and clinical remission for csDMARD-IR patients with RA [46]. The mechanism by which JAK inhibitors improve mental health, on the other hand, is not well understood. Currently available JAK inhibitors differ largely in their selectivity for distinct JAK receptors. Nonetheless, the selectivity that provides the best therapeutic impact while causing the least toxicity is unknown. Our findings indicate that tofacitinib, which targets JAK-3, improves SF-36 scores the most, speculating that JAK-3 inhibition may have the potential to alleviate depression symptoms in RA. However, there is a lack of evidence to substantiate this claim, which is beyond the scope of this review. Studies showed that stress activates JAK-3 in part through the acid sphingomyelinase, and inhibiting this enzyme reduces Jak-3 phosphorylation and improves hippocampal neurogenesis in mice [16]. However, a definitive conclusion cannot be reached in this regard because there appear to be no specific clinical trials that evaluated the therapeutic efficacy of JAK inhibitors for the treatment of depression in RA. Most of the RA clinical trials frequently use SF-36 to assess mental health. While this measure compares mental and physical QoL outcomes, it is important to note that the SF-36 MCS is a broader concept of HRQoL that is not limited to mental health. Despite the fact that the SF-36 assesses depression and anxiety, standard depression and anxiety scales may be required to find out the precise effect of JAK inhibitors on mental health. Therefore, future research on these newer RA treatments should focus on using specific tools to measure depression or anxiety.

Our meta-analysis included only phase 2 or 3 RCTs, indicating that included patients were

closely monitored for an extended period and patient-reported outcomes are frequently assessed. By quantifying responses with MCID values, clinically meaningful outcomes are obtained. The findings indicate that JAK inhibitor therapy improves mental health and overall HRQoL in patients with RA. These improvements in HRQoL associated with treatment are critical for patients and may aid policymakers in making decisions.

Several limitations are acknowledged. JAK inhibitors have been shown to improve HRQoL and symptoms in patients with RA who have failed to respond to first-line therapies such as MTX. This study analyzed SF-36 scores at baseline and at the most recent follow-up; data from other time points were not analyzed. Because of the lack of prior DMARD therapy stratification, the effect of JAK monotherapy on mental health outcomes could not be determined in few studies. Patients on placebo were switched to an intervention drug after 3 or 6 months in a few studies. Therefore, the effect of JAK inhibitors and placebo on mental health could not be compared at the maximum follow-up duration of these studies. The overall heterogeneity of the study could not be explained by subgroup analysis based on follow-up duration or clinical trial phase. Additional factors that contribute to overall heterogeneity must be identified. Certain studies were excluded because of our inability to obtain complete texts. While the funnel plot revealed no evidence of publication bias, it may be possible that insignificant mental health outcomes have been omitted.

CONCLUSIONS

In conclusion, JAK inhibitors therapy, both as monotherapy as well as in combination with MTX, results in a clinically relevant improvement in the mental health of the RA patients. More studies using specific measures to assess depression and anxiety outcomes are needed in the future to have a better insight of JAK inhibitors' impact on the mental health of RA patients.

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