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Systematic Review and Meta-analysis of Interventions for Depression and Anxiety in Persons With Rheumatoid Arthritis

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Background: Psychiatric comorbidities, such as depression and anxiety, are very common in persons with rheumatoid arthritis (RA) and can lead to adverse outcomes. By appropriately treating these comorbidities, disease-specific outcomes and quality of life may be improved.

Objective: The aim of this study was to systematically review the literature from controlled trials of treatments for depression and anxiety in persons with RA.

Methods: We searched multiple online databases from inception until March 25, 2015, without restrictions on language, date, or location of publication. We included controlled trials conducted in persons with RA and depression or anxiety. Two independent reviewers extracted information including trial and participant characteristics. The standardized mean differences (SMDs) of depression or anxiety scores at postassessment were pooled between treatment and comparison groups, stratified by active versus inactive comparators.

Results: From 1291 unique abstracts, we included 8 RA trials of depression interventions (6 pharmacological, 1 psychological, 1 both). Pharmacological interventions for depression with inactive comparators (n = 3 trials, 143 participants) did not reduce depressive symptoms (SMD, −0.21; 95% confidence interval [CI], −1.27 to 0.85), although interventions with active comparators (n = 3 trials, 190 participants) did improve depressive symptoms (SMD, −0.79; 95% CI, −1.34 to −0.25). The single psychological trial of depression treatment in RA did not improve depressive symptoms (SMD, −0.44; 95% CI, −0.96 to 0.08). Seven of the trials had an unclear risk of bias.

Conclusions: Few trials examining interventions for depression or anxiety in adults with RA exist, and the level of evidence is low to moderate because of the risk of bias and small number of trials.

Key Words: anxiety, depression, meta-analysis, rheumatoid arthritis, systematic review

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Rheumatoid arthritis (RA) is a chronic immune-mediated arthropathy that affects more than 1.3 million Americans[1,2] and more than 15 million people worldwide.[3] Because the peak age at onset is in the fourth and fifth decades of life, RA affects individuals in the prime of their lives from social and work perspectives and is associated with considerable disability.[4–6] Depression will affect up to 66% and anxiety up to 70% of individuals with RA,[7–9] and almost 17% of persons with RA have a current major depressive disorder.[10]

Psychiatric comorbidity is associated with adverse outcomes in RA. In persons with RA, depression is associated with higher levels of pain and disability, lower health-related quality of life (QOL), and increased mortality.[11–13] Depression is a greater predictor of work disability in early arthritis than both disease activity and response to treatment.[14] Symptoms of depression and anxiety are associated with increased disease activity, a reduced response to RA symptom treatment, and a decreased likelihood of achieving RA symptom remission.[15] Managing depression and anxiety may be a means of improving outcomes in persons with RA, but commonly used pharmacological treatments for depression may be less effective in persons with RA who use anti-inflammatory therapies[16] or lead to potentially harmful adverse effects or exacerbations in symptoms.[17]

The primary objective of this systematic review and meta-analysis was to identify the existing literature pertaining to controlled trials of pharmacological and psychological interventions for depression and anxiety in persons with RA.

MATERIALS AND METHODS

We conducted this systematic review using an a priori published protocol,[18] according to the approach described in the Cochrane Handbook for Systematic Reviews. We report the findings according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) criteria.[19,20]

Populations, Interventions, Comparators, Settings, and Study Designs

As symptoms of depression and anxiety are very common, a threshold at which treatment may be initiated must be established, to ensure that only those who could benefit from treatment are exposed to the potential risks of therapies and to ensure that symptoms were severe enough that treatment could have an effect. Therefore, we included trials conducted in persons with RA who were depressed and/or anxious to ensure that effects were assessed in the population in which the intervention would later be applied. Rheumatoid arthritis was defined according to the criteria reported in each article. Eligible trials were controlled clinical trials (i.e., randomized controlled trials [RCTs], controlled before and after trials) conducted in any clinical setting. Diagnoses of depression or anxiety could be identified based on a clinical interview or self-report using a screening tool. There were no other prespecified criteria regarding the definition of depression or anxiety, and we examined the methods used by individual papers to identify the study populations, including the instruments used. We excluded trials if the entire sample was younger than 18 years to reduce heterogeneity.

Outcome Measures

We identified 1 primary research question: "What is the efficacy of pharmacological and psychological treatments for depression or anxiety in persons with RA?" Based on recommendations from primary care providers and individuals living with RA, we included the following secondary outcomes: (1) difference in fatigue scores at postassessment between the treatment and comparison groups, (2) difference in QOL scores at postassessment between the treatment and comparison groups, (3) difference in pain scores at postassessment between the treatment and comparison groups, and (4) the proportion of participants achieving 50% reduction or greater in depressive or anxious symptoms from baseline to postassessment between the treatment and control. In all cases, postassessment was the longest reported follow-up.

The tolerability of pharmacotherapy for depression or anxiety in RA was examined according to the dose and duration of the treatment, dropout rates, and any reported adverse effects.

Search Strategy

Our search strategies (see lists, Supplemental Digital Content 1, http://links.lww.com/RHU/A65 which detail the searches) were developed with the help of a medical librarian (M.F.) and experts in rheumatic disease (C.A.H., C.A.P.) and psychiatric disorders (S.B.P., J.W., L.G., K.M.F., J.S., J.B.). We identified RCTs and related systematic reviews using the Cochrane Database of Systematic Reviews and the following databases: MEDLINE, EMBASE, PsycINFO, PsycARTICLES Full Text, Cochrane Central Register of Controlled Trials, CINAHL, Web of Science, and Scopus. To identify completed or ongoing trials, we searched Clinicaltrials.gov and the World Health Organization trial register. To identify additional citations, we searched the reference lists of related systematic reviews and of the included trials. There were no date or language limits placed on the searches. Databases were searched from inception date to March 25, 2015. The Cochrane Highly Sensitive Search Strategy was used in MEDLINE, and variations of this filter, or other validated filters, were used for other databases.

Study Selection Process

EPPI-Reviewer[21] was utilized for the 2-phase title and abstract review by 2 independent reviewers (K.M.F. and R.A.M.). Titles and abstracts were reviewed in the first phase to determine if they were conducted in individuals with RA and who had depression or anxiety. In the second phase, these abstracts were determined to be clinical trials or not. Subsequently, the same reviewers also independently reviewed full-text articles in detail to ensure all inclusion criteria were met, and disagreements were resolved by discussion.

Data Extraction and Management

Data collection was completed by 2 independent reviewers using a data collection tool developed by the author team and implemented in EPPI-Reviewer. We extracted information on study design, inclusion criteria for the study population including demographic or disease characteristics (e.g., age, sex, disease subtype, race/ethnicity), methods for identifying psychiatric comorbidity (e.g., diagnostic interview, self-report questionnaire) including the tools used, interventions used, items related to the risk of bias assessment (see below), and any efficacy or safety outcomes. We sought translation for the non-English articles.

Risk of Bias Assessment and Grading the Evidence

The internal validity of the trials was independently evaluated by 2 reviewers using the Cochrane Collaboration's Risk of Bias tool.[22] This tool evaluates risk of bias in 6 domains: sequence generation; allocation concealment; masking/blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Each domain is rated as having either a low risk of bias, unclear risk of bias, or high risk of bias. The overall assessment is based on responses to individual domains; the overall score was rated as having a high risk of bias if 1 or more individual domains is assessed as having a high risk of bias. Only if all components are rated as having a low risk of bias is the overall risk rated as low. Risk of bias for all other studies was rated as unclear. Disagreements on the bias assessment were resolved by discussion. The approach described by the GRADE working group was used to determine the strength of the evidence: low, moderate, or high.[23]

Data Synthesis and Analysis

Descriptive statistics, including mean, median, SD, interquartile range, and frequencies (reported as a percent), were used to summarize the study findings. Because the tools used to measure depression differed between trials, we chose the standardized mean difference (SMD) as the outcome measure. We calculated the SMD using depression or anxiety scores on any depression or anxiety tool at postassessment between the treatment and comparison groups. The size of the effect was measured in SD units. Small, medium, and large effects are represented by SMDs of 0.20, 0.50, and 0.80, respectively.[24] In the context of these analyses, a negative SMD indicates an improvement of symptoms in favor of the intervention (except in the instance of QOL, where a positive SMD indicates improvement). Because the proportion achieving a 50% reduction in symptoms was a categorical outcome, an odds ratio with 95% confidence intervals (95% CIs) was calculated to compare groups.

Summary effect measures were generated using Review Manager (RevMan 5.3).[25] Analyses are presented overall and

stratified by the type of comparison group used: active (i.e., another form of psychotherapy or pharmacotherapy) or inactive (placebo, wait-list control, usual care). For the sole 3-arm trial identified, we included only 1 comparison (cognitive behavioral therapy [CBT] vs. sertraline) in the meta-analysis.[26] Heterogeneity was quantified using the I^2 statistic, and its significance determined by the Q P value. I^2 is calculated directly from the Q statistic; I^2 of 0% indicates the absence of observed heterogeneity, whereas values of 25%, 50%, and 75% translate to low, medium, and high heterogeneity, respectively.[27] All pooled estimates were calculated using a random-effects model with the accompanying 95% CI. Metaregression was not conducted because of the small number of eligible studies (i.e., <10).[28] R v3.1.1[29] was used to assess publication bias using funnel plots, Begg rank test,[30] or Egger's regression test.[31]

RESULTS

Results of the Search

We initially screened 1291 unique abstracts and excluded 1251 in the first phase. The majority (58%) were excluded because they did not report on a population with RA (721/1251), whereas a further 380 (30%) did not report on a group with depression or anxiety, and finally, 150 (12%) did not study depression or anxiety (Fig. 1, Supplemental Digital Content 2, http://links.lww.com/RHU/A66). After the second phase, where 24 more abstracts were excluded (13/24 were not conducted in persons with depression or anxiety, and 11/24 were not clinical trials), the full texts of 16 articles were reviewed, of which 8 met all inclusion criteria (Table). The age restriction exclusion criteria (no studies including those <18 years old) did not result in the exclusion of any studies.

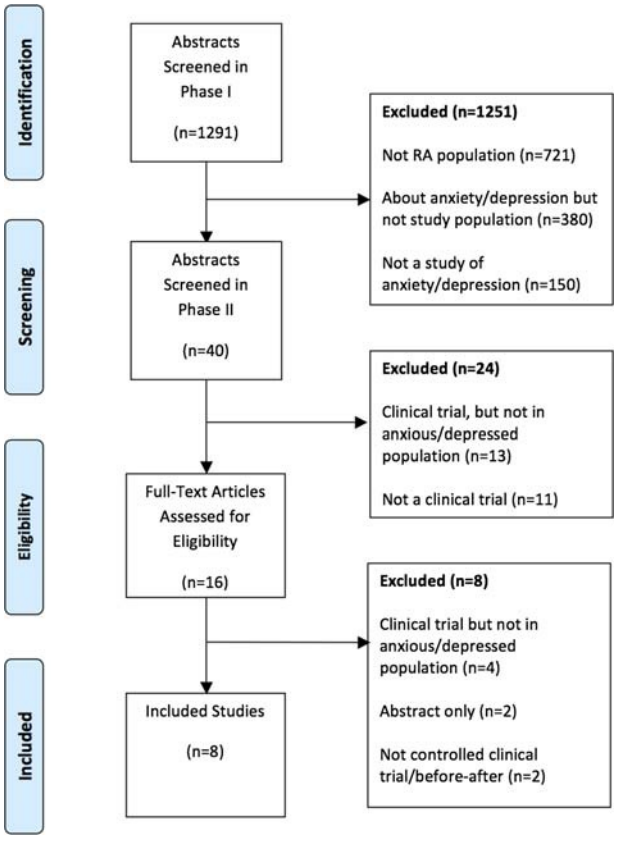

FIGURE 1. Study flow diagram.

Description of Trials

All trials were RCTs that investigated treatments for depression (i.e., none investigated anxiety as the primary outcome) and were published between 1986 and 2008 in Europe (n = 4),[32–35] North America (n = 2),[26,36] or Asia (n = 2).[37,38] The number of participants in the included trials ranged from 36 to 188 (mean, 74.8 [SD, 56.3]). Most trials (n = 6) assessed the effect of pharmacotherapy,[32–34,36–38] one investigated a psychological intervention,[35] and another trial used a combined pharmacological and psychological approach.[26] All trials investigated the effect of the intervention on symptoms of depression as the primary outcome, and 3 assessed anxiety as a secondary outcome.[26,32,35] Eight different instruments were used to measure depression in the included trials (Table). Five of the 6 studies[26,32,35,37,38] published after the 1987 release of the American College of Rheumatology diagnostic criteria[39] used it as such. The 2 studies[34,36] published prior to/in 1987 used the 1958 American Rheumatism Association (ARA) diagnostic criteria,[40] and the final study[33] used the 1982 criteria from the ARA.[41]

Interventions and Assessments

The duration of treatment in the included trials ranged from 3 to 24 weeks (mean, 11.5 [SD, 7.0] weeks). Three of the 6 pharmacological trials compared the medication with placebo,[32,34,36] one compared the effects of 2 medications,[33] and 2 others compared the effects of 2 Chinese herbs.[37,38] The examined medications were dothiepin, S-adenosylmethionine (SAMe), trimipramine, paroxetine versus amitriptyline, Xingfeng capsule versus Zhengqing Fengtongning capsule, and Xingfeng capsule versus Fengshigutong capsule. The psychological intervention compared individualized CBT with usual care,[35] and the combined pharmacological/psychological trial examined the use of sertraline alone as compared with sertraline combined with either CBT or attention-control therapy.[26]

The most commonly used tool to assess depression as an outcome was the Hamilton Rating Scale for Depression (HAM-D), used in 3 of 8 trials.[26,32,34] Anxiety was assessed as a secondary outcome in 3 trials, using the Hospital Anxiety and Depression Scale (HADS),[32] Impact of Rheumatic Diseases on General Health and Lifestyle (IRGL) anxiety scale,[35] and the State-Trait Anxiety Inventory.[26] All trials examined the effect of the intervention on pain, and QOL was assessed in 3 trials.

Most RA trials (n = 5) used a single tool to determine trial eligibility, including the Self-rating Depression Scale (n = 2), the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[26] (n = 1), Zung's Self-rating Depression Scale[36] (n = 1), or IRGL questionnaire (n = 1).[35] The remaining 3 RA trials used multiple methods to assess trial eligibility; 2 trials used a clinician assessment and either the HADS[32] or the HAM-D,[34] whereas the study by Bird and Broggini[33] used *International Classification of Diseases, 10th Revision* codes and the Montgomery-Åsberg Depression Rating Scale (MADRS).

Other depression tools used to assess outcomes were the HADS, MADRS, IRGL depression scale, Zung's Self-rating Depression Scale, the Center for Epidemiologic Studies Depression Scale, the Geriatric Depression Scale, and the Self-rating Depression Scale.

Risk of Bias Assessment

Seven of the RA trials had an unclear risk of bias, whereas the final RA trial had a high risk of bias due to failures of blinding (see Figure and Table, Supplemental Digital Content 3, http://

TABLE. Included Studies

Author (Year) Recruitment Setting	Study Information	Psychiatric Comorbidity Information	Intervention			Outcomes			
			Intervention	Comparator	Duration	Primary Outcome Measures	Secondary Outcome Measures	Outcome	Tolerability
Ash et al.[32] (1999) **Setting** Rheumatology clinic	**Study design** Randomized controlled trial Females only **Disease stability required pre-enrollment** Excluded if: • HAQ <1 • Acute flare in RA symptoms • Taking oral steroids in dose of prednisolone >7.5 mg daily or the equivalent • Received an intra-articular steroid injection within the previous 1 month, • Changed second-line therapy within the previous 4 mo • Changed NSAIDs within the previous 1 month **Age:** 18–70 y **Disease Duration:** 6.5 y (dothiepin group); 10 y (placebo group) **Seropositivity**: 68% (dothiepin group); 78.3% (placebo group) **Ritchie Articular Index (RAI)**: 12.0 (dothiepin group); 14.0 (placebo group)	**Classification** Depressive disorder based on clinical assessment **Screening tool** HADS ≥*8 on either subscale or a total score of* ≥*12*	**Pharmacologic** Dothiepin 75mg for the first 2 wk 150 mg daily for the following 8 wk (n = 22)	Placebo (n = 23)	12 wk (11 wk of medication)	HADSHAM-D	HADS Visual analog scale (pain)	Difference in mean scores	
Bird and Broggini[33] (2000) **Setting** Specialty clinic	**Study design** Randomized controlled trialRA for at least 1 y, defined according to the ARA criteria, and score of 1–3 on Steinbrocker Functional Classification **Disease stability required pre-enrollment** • Concomitant medications for RA permitted but had to be started at least 3 mo before study (corticosteroids, NSAIDs, gold, azathioprine, D-penicillamine, sulfasalazine, chloroquine, cyclophosphamide) • RA stable for at least 3 mo prior to study **Exclusion criteria:** • Patients who posed a suicide risk • Patients who had received antidepressant treatment within 8 wk of study initiation (including monoamine oxidase inhibitors, lithium, electric convulsive therapy, selective serotonin reuptake inhibitors, tricyclic or tetracyclic antidepressants) • Patients with renal, hepatic, gastrointestinal, or cardiovascular disease, neurological or metabolic disorders, glaucoma, prostatic hypertrophy, or urinary retention **Age:** 18–70 y **Clinical Global Impression Score:** 3.6 (paroxetine group); 3.6 (amitriptyline group) **RAI**: 21.5 (paroxetine group); 21.8 (amitriptyline group) **Concomitant medications:** anti-inflammatory drugs: 74.5% (paroxetine group); 72.3% (amitriptyline group); corticosteroids: 40.4% (paroxetine group); 27.7% (amitriptyline group)	**Classification** Mild, moderate or severe depression per *International Classification of Diseases, 10th Revision* criteria **Screening tool** MADRS*Score of* ≥*16*	**Pharmacologic** Paroxetine (20–40 mg daily) (n = 94)	Amitriptyline (75–150 mg daily) (n = 94)	8 wk	MADRS	Global Pain Rating Health Assessment Questionnaire (QOL)	Difference in mean scores Remission response rate of ≥50% at end of treatment	Rate of adverse effects
Caruso et al.[34] (1987)	**Study design** Randomized controlled trial Definite or classic RA per ARA Criteria No history of depressive symptoms before RA onset **Exclusion criteria:** • No clinically significant abnormality to the liver, cardiocirculatory apparatus, or kidney **Disease stability required pre-enrollment** Adequate and stable dosage of antiarthritis and anti-inflammatory drugs **On DMARDs**: 21 patients taking gold compounds, 15 NSAIDS, 10 chloroquine, 7 steroids, 7 D-penicillamine **Disease duration**: 8.3 y (SAMe group); 8.5 y (placebo group)**Functional stage**: Stage I (0%), stage II (60%), stage III (40%) (SAMe group); stage I (6.9%), stage II (34.5%), stage III (37.9%) (placebo group)	**DSM classification** Major depression *Based on DSM-III* **Screening tool** HAM-D ≥*35 and no symptom rated 1*	**Pharmacologic** SAMe 200 mg intramuscularly (30) **Provider delivering intervention** Physician	Placebo (n = 29)	3 wk	HAM-D	Visual analog scale (pain)	Difference in mean scores	Discontinuation rate Rate of adverse effects

Evers et al.[35] (2002)	**Study design** Randomized controlled trial RA according to the ACR criteria **Age:** ≥18 y **Setting:** 3 Outpatient rheumatology clinics **Exclusion criteria:** • Patients with comorbid conditions that might interfere with CBT treatment (including malignancy, cardiac, respiratory, hepatic, and renal insufficiency) **Disease duration**: 2.7 y (CBT group); 3.5 y (usual care group) **Disease Activity Score**: 3.23 (CBT group); 3.00 (usual care group) **Functional Disability**: 2.41 (CBT group); 2.44 (usual care group) **On DMARDs**: (type not specified) 90% (CBT group); 97% (usual care group); using NSAIDs 73% (CBT group); 83% (usual care group)	Questionnaires to determine risk profiles. At risk in upper 30% in anxiety or negative mood with score in upper 30% on at least 2 of 6 cognitive behavioral factors: illness cognitions of heightened helplessness, low levels of acceptance, passive manner of coping with stress, passive manner of coping with pain and low levels of social functioning.	**Psychological** Cognitive behavioral therapy (CBT) (n = 30) **Provider delivering intervention** Therapist supervised by cognitive behavior supervisor	Usual care(Standard medical care from rheumatologist and quarterly consultation with rheumatology consultant) (n = 29)	6 mo	Impact of Rheumatic Diseases on general Health and Lifestyle Negative Mood Scale	Impact of Rheumatic Diseases on general Health and Lifestyle Anxiety Scale Impact of Rheumatic Diseases on general Health and Lifestyle Pain Scale	Difference in mean scores	Discontinuation rate
Liu et al.[37] (2007)	**Study design** Randomized controlled trial **Disease stability required pre-enrollment** • Meet ACR 2010 revised criteria • Receive a stable dose of NSAID does during the 4 wk prior to screening (or not take them 1 wk prior) • Not taking disease-modifying drugs during the 4 wk prior to screening • Anyone with a dose of ≤10 mg prednisone or equivalent has been taking it for at least 4 wk • Cannot have received intra-articular or systemic corticosteroid injections in the previous 4 wk • Cannot have high disease activity (DAS 28–3 score >5.1) • Cannot have other chronic inflammatory or connective tissue disease • Cannot have severe cardiovascular disease • Cannot be pregnant or breast feeding **Age:** 18–65 y **Setting** Outpatient clinics Inpatient hospital departments	**Classification** Depression **Screening tool** Self-rating depression scale	**Nonpharmacologic** Xingfeng capsule (n = 40)	Zhengqing Fengtongning capsule (n = 36)		Self-rating depression scale	Unable to determine from translation	Difference in mean scores	
Liu et al.[38] (2008)	**Study design** Randomized controlled trial **Disease stability required pre-enrollment** • Meet ACR 2010 revised criteria • Receive a stable dose of NSAID does during the 4 wk prior to screening (or not take them 1 wk prior) • Not taking disease-modifying drugs during the 4 wk prior to screening • Anyone with a dose of ≤10 mg prednisone or equivalent has been taking it for at least 4 wk • Cannot have received intra-articular or systemic corticosteroid injections in the previous 4 wk • Cannot have high disease activity (DAS 28–3 score >5.1) • Cannot have other chronic inflammatory or connective tissue disease • Cannot have severe cardiovascular disease • Cannot be pregnant or breast feeding **Age**: 18–65 y **Setting** Outpatient clinics Inpatient hospital departments	**Classification** Depression **Screening tool** Self-rating depression scale	**Nonpharmacologic** Xingfeng capsule (n = 35)	Fengshigutong capsule (n = 25)		Self-rating depression scale	Unable to determine from translation	Difference in mean scores	
Macfarlane et al.[36] (1986)	**Study design** Randomized controlled trial Definite or classic RA as defined by the ARA, seropositive for rheumatoid factor, and had bony erosions on X-ray **Exclusion criteria:** Evidence of tender trigger points **Setting** Specialty clinic **Functional class:** 2.1 (trimipramine group); 2.0 (placebo group) **RAI**: 19.7 (trimipramine group); 22.8 (placebo group)	**Screening tool** Zung's Self Rating Depression Scale ≥51	**Pharmacologic** Trimipramine (25 mg first week, 25 mg 2x daily second week, 25 mg 3× daily remaining wk) (n = 13) **Provider delivering intervention** Rheumatologist	Placebo (n = 14)	12 wk	Zung's Self Rating Depression Scale	5-point scale (pain)	Difference in mean scores	Discontinuation rate Rate of adverse effects

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TABLE. *(Continued)*

Author (Year) Recruitment Setting	Study Information	Psychiatric Comorbidity Information	Intervention			Outcomes			
			Intervention	Comparator	Duration	Primary Outcome Measures	Secondary Outcome Measures	Outcome	Tolerability
Parker et al.[26] (2003)	**Study design** Randomized controlled trial RA according to 1987 ACR criteria **Exclusion criteria:** • History of organic brain syndrome, presence of a psychotic disorder, presence of other uncontrolled medical disorders • Presence of a therapeutic dosage of an antidepressant medication • Presence of another autoimmune disorder or disabling condition • Classified as functional class IV according to Steinbrocker criteria **Setting** Rheumatology clinic VA hospital, University Medical Center **Disease duration**: 12.6 y (overall) **Functional class**: Class I (4%); class II (48%); class III (48%) (overall) **Disease Activity (Rapid Assessment of Disease Activity in Rheumatology):** 5.4 (overall) **On DMARDs**: NSAIDS: 76% (CBT/sertraline group); 95% (attention-control/ sertraline group); 82% (sertraline group); noncytotoxic DMARDS (i.e., gold, penicillamine, sulfasalazine, hydroxychloroquine): 41% (CBT/sertraline group); 55% (attention-control/sertraline group); 35% (sertraline group); cytotoxic DMARDs (i.e., methotrexate, azathioprine, cyclosporine, cyclophosphamide): 65% (CBT/sertraline group); 50% (attention-control/sertraline group); 53% (sertraline group); corticosteroids: 59% (CBT/sertraline group); 45% (attention-control/sertraline group); 65% (sertraline group)	**DSM Classification** Major depression based on Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*	**Pharmacologic/ nonpharmacologic** Groups: (1) CBT/sertraline (n = 14) (2) Attention-control/sertraline (n = 13) (3) Only sertraline (n = 14) **Provider delivering intervention** Psychiatrist Psychologist	Groups: (1) CBT/sertraline (n = 14) (2) Attention-control/ sertraline (n = 13) (3) Only sertraline (n =(14)	10 wk	Center for Epidemiologic Studies Depression scaleHAM-DGeriatric Depression Scale	State-Trait Anxiety Inventory Visual analog scale (Pain) McGill Pain Questionnaire	Difference in mean scores	Discontinuation rate

DAS indicates Disease Activity Score.

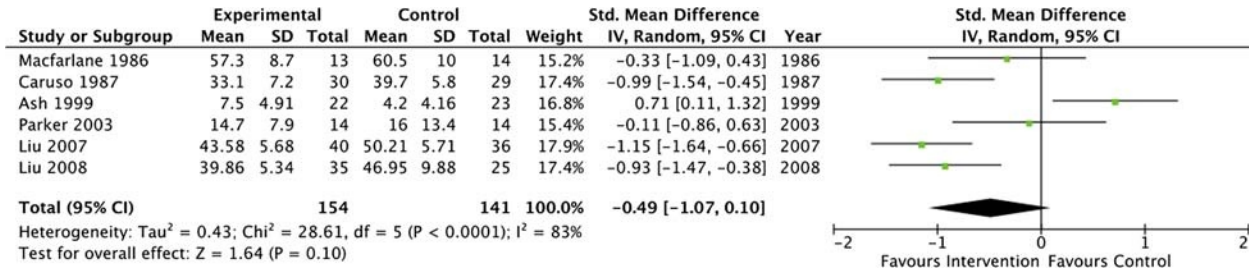

FIGURE 2. Overall forest plot of pharmacological treatments for symptoms of depression.

links.lww.com/RHU/A67 and 4, http://links.lww.com/RHU/A68 for risk of bias assessment).

Primary Outcomes

Depression

Overall, interventions for depression in RA (n = 6 trials, 295 participants) did not result in a reduction in depressive symptoms (SMD, −0.49 [95% CI, −1.07 to 0.10]) (Fig. 2). There was significant heterogeneity between estimates: I^2 = 83%, Q P < 0.0001. When pharmacological trials were stratified by whether the comparator was an active treatment (such as an antidepressant medication) or inactive comparison (placebo), interventions with an active treatment comparison (n = 3 trials, 164 participants) were associated with a reduction in depressive symptoms (SMD, −0.79 [95% CI, −1.34 to −0.25]) (Fig. 3A). There was no improvement in depressive symptoms for those pharmacological trials using an inactive comparator (n = 3 trials, 131 participants) (SMD, −0.21 [95% CI, −1.27 to 0.85]) (Fig. 3B). Stratification by treatment comparator did not reduce the amount of heterogeneity present for inactive comparators (I^2 = 88%, Q P < 0.0001), although it did for trials with active comparators (I^2 = 62%, Q P < 0.0001). When analyzed separately, the 2 trials using a Chinese herbal supplement were effective in reducing symptoms of depression (SMD, −1.05 [95% CI, −1.41 to −0.69]). The trial by Ash et al.[32] may have included persons with subthreshold depression (resulting in less room for improvement); the analysis was repeated without this trial, and following this depressive symptoms showed improvement (SMD, −0.78 [95% CI, −1.14 to −0.42]).

The single psychological therapy trial of depression treatment in RA showed no improvement in depressive symptoms (SMD, −0.44 [95% CI, −0.96 to 0.08]).

Anxiety

Anxiety symptoms did not improve in any trial of depression treatment (pharmacological or psychological), regardless of the comparison group used: a single trial with an active comparator (SMD, 0.24 [95% CI, −0.51 to 0.98]) and 2 trials with inactive comparators (SMD, −0.11 [95% CI, −1.01 to 0.79]).

Strength of Evidence

There was a range in evidence strength in the included trials: 4 trials were moderate quality, 2 trials were high quality, 1 trial was low quality, and 1 trial was very low quality (see Table, Supplemental Digital Content 5, http://links.lww.com/RHU/A69 for ratings). Overall, the body of evidence for depression interventions in RA was of moderate strength.

Secondary Outcomes

Depression

In the single RCT that reported on the proportion of patients achieving 50% reduction or greater in symptoms,[33] there was no difference between the 2 active pharmacological treatments (P = 0.296).

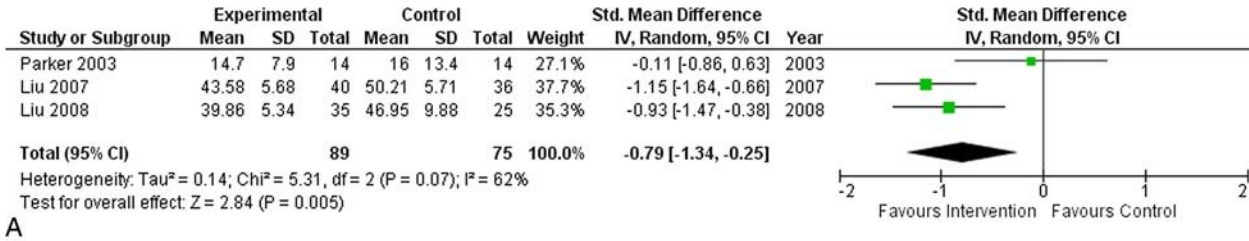

FIGURE 3. A, Forest plot of pharmacological treatments with active comparators for symptoms of depression. B, Forest plot of pharmacological treatments with inactive comparators for symptoms of depression.

Pain

Pain scores in RA did not improve in 3 trials of depression interventions with an active comparator (SMD, −0.05 [95% CI, −0.36 to 0.25]) or in 3 trials with an inactive comparator (SMD, −0.60 [95% CI, −1.22 to 0.03]).

Fatigue

Fatigue was not reported as an outcome in any of the trials.

Quality of Life

Quality of life in RA did not improve in 2 trials of depression interventions with an active comparator (SMD, −0.22 [95% CI, −1.03 to 0.59]) or a single depression intervention trial with an inactive comparator (SMD, 0.02 [95% CI, −0.57 to 0.60]).

Tolerability

Three RA trials reported on adverse medication effects;[33,34,36] the trial comparing paroxetine to amitriptyline reported more adverse events in the amitriptyline group,[33] whereas nausea was more common in the placebo group of the trimipramine trial[36] (see Table, Supplemental Digital Content 6, http://links.lww.com/RHU/A70 for adverse effects). The dropout rates in the treatment groups of the RA trials ranged from 0.0% to 35.0%.

Publication Bias

Significant publication bias was not detected on any primary or secondary outcomes for the included trials analyzed using both Begg and Egger tests. All funnel plots appeared symmetrical based on visual inspection.

DISCUSSION

In our systematic review of the literature, we found only 8 RCTs reporting on interventions for treating depression in RA and none reporting on interventions for anxiety in RA. Among pharmacological interventions, only those with an active comparison group were effective in reducing symptoms of depression in RA. Some trials either did not report the effects of the interventions on fatigue, pain, or QOL or did not report a statistically significant benefit in those domains. The sole study of a psychological intervention alone showed benefit for treating depression, but this did not reach statistical significance.

Most of the included trials examined the use of pharmacological interventions for treating depression; those trials using active comparators were effective in reducing symptoms of depression. No interventions for depression were effective in reducing symptoms of anxiety. Trimipramine, sertraline, and CBT are conventional treatment strategies for depression, whereas dothiepin is not available in North America, SAMe is not a first-line treatment for depression, and the specific Chinese herbal supplements are not widely available in other countries for treatment of depression. The 2 trials of Chinese herbal supplements included persons with low disease activity and those not treated with disease-modifying antirheumatic drugs (DMARDs); therefore, these study populations may not be representative of the typical RA patient. The pooled estimate of these trials should be interpreted with caution, as most do not utilize treatment methods that are currently in wide use; the evidence to support pharmacotherapy for depression treatment in RA is therefore limited. There is a dearth of studies exploring the effects of controlled interventions for anxiety in persons with RA, although anxiety has numerous negative effects in persons with RA, including greater fatigue[11] and increased disease activity.[15]

It is necessary to explore the use of these treatments for depression and anxiety in RA specifically, as affected persons may respond differently to treatment or experience disease-specific adverse effects (or more severe adverse effects). Psychotropic medications may exacerbate already elevated levels of fatigue.[42] There may also be interactions between and treatments commonly used for depression in RA and DMARDs or other anti-inflammatory therapies. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants in combination with nonsteroidal anti-inflammatory drugs (NSAIDs) commonly used in RA may impair platelet function, increasing the risk of gastrointestinal and intracranial bleeding.[43,44] Some commonly used SSRIs (i.e., escitalopram, citalopram) may also confer an increased risk of bleeding when used in combination with 5-aminosalicylic acid.[45] A post hoc analysis of a large clinical trial revealed that persons using NSAIDs were less likely to achieve remission on SSRI therapy, compared with those not using NSAIDs, possibly by altering cytokine and other regulatory protein concentrations.[16] One study showed less frequent mood and anxiety disorders in patients on tumor necrosis factor inhibitors compared with those on nonbiological or no DMARDs.[46] This effect has not been studied with other biologic DMARDs but may reflect the greater effectiveness of these newer drugs, with demonstrated greater improvement in disease activity and QOL. In 2 of the 3 studies published since the introduction of biologic DMARDs (ranging from 2003 to 2008), participants were ineligible for inclusion if they were on DMARDs, and in the other study, no participants were on biologic DMARDs. Given the increasingly widespread use of biologic DMARDs, future intervention studies will need to consider the potential for such disease-treatment interactions.

The trials included in this review used 8 different scales to measure symptoms of depression in RA, most using the HAM-D. The validity of these depression scales has not been assessed in a sample with RA, although many have been validated in the general population. A recent systematic review of the prevalence of depression in RA recommended validating the commonly used depression tools and specifically assessing the cutoff points to define depression.[10] It is imperative that depression and anxiety screening tools be validated in disease-specific settings to ensure scale performance is adequate; investigate potential confounding effects, including those of somatic symptoms; and assess the optimal scoring criteria.

Based on the GRADE system, the strength of the evidence from RA trials was moderate. All but 1 RA trial had an unclear risk of bias; the remaining RA trial was rated as a high risk of bias due to a lack of blinding. The overall strength of the evidence was lower, and risk of bias higher, in psychological trials. In psychotherapy interventions, the ability to adequately blind participants, outcome assessors, and investigators is limited because of the nature of the intervention; blinding may not be necessary, however, and there are proposed methods for how to minimize bias related to this complex issue.[47] The RA trials using active comparators were published more recently and had a larger number of participants than those using inactive comparators. In addition, 2 of the 3 trials with active comparators included participants with low disease activity, differing somewhat for the trials without active comparators. These and other differences in the patient populations may also account for the differences observed and may account for finding benefit in trials with active comparators and not in those with inactive comparators. Significant statistical heterogeneity was present between pooled estimates of pharmacotherapy, anxiety, and QOL. This reduces the confidence in our findings, and the estimates should be interpreted cautiously.

As depression and anxiety affect treatment responses to RA-specific therapies[14] and adversely affect mortality and QOL,[11–13] it is essential to adequately and appropriately treat

these comorbidities. Our findings highlight paucity of information to support clinicians treating depression and anxiety in RA and underscore the urgent need for further intervention trials in the area of psychiatric comorbidity in RA to inform clinical care. Furthermore, as depression and anxiety are chronic health conditions, it is important for future trials to be conducted with extended follow-up periods to determine effectiveness over the long term. We convened advisory groups to identify outcomes aside from the psychiatric ones that are important to patients and practitioners (pain, fatigue, and QOL). Despite their perceived importance, it is unclear what interventions might have the greatest impact on these domains. Drugs used to treat depression and anxiety may have pharmacodynamic effects on the underlying chronic inflammatory disease, which might be best captured with other outcomes. Similarly, psychotherapy in depression and anxiety may have different outcomes in persons with immune diseases than in persons without them. It is possible the distress caused by the chronic disease itself or the ongoing inflammatory state may render the psychiatric comorbidity more difficult to treat. This needs to be studied.

The next trials in the area of psychiatric comorbidity in RA should include measures of outcomes in the psychiatric comorbidity and the immune disease under study. It is critical to understand the evolution of the underlying immune disease while the psychiatric illness is treated. To fully understand if there are specific features of RA that are associated with a greater burden of depression and anxiety, to determine the optimal instruments that best identify these conditions in RA, and to determine if there are relevant biomarkers, prospective cohort studies should be undertaken so that future clinical trials can be purposefully planned.

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Morning Calm – Waiting for the ferry in Port Townsend, WA