The temporal relationship between depression and rheumatoid arthritis disease activity, treatment persistence and response: a systematic review

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Abstract

Objective. To determine whether depression has a temporal association with RA disease activity, treatment persistence and response to therapy.

Methods. We performed a systematic review encompassing an electronic database search of all published literature since the availability of biologic response modifiers (beginning in 1998) investigating the impact of depression on downstream RA disease progression and treatment.

Results. Only seven articles that evaluated temporal relationships between depression and RA outcomes comprising disease activity, treatment persistence and response to therapy, were included in the review. Results from these studies suggest that depression may exacerbate pain and disease activity and decrease the efficacy of pharmacological (i.e. biologic and non-biologic DMARDs) and some non-pharmacological (e.g. cognitive behavioural therapy) RA treatments.

Conclusion. Given the available evidence, depression probably has a temporal influence on RA disease progression and treatment. However, it is unclear whether these observed effects are due to a response tendency on patient-reported outcomes created from negative cognitive perceptions, immunologically mediated processes that increase inflammation or behavioural changes that lead to decreased physical activity and a greater sensitivity to pain.

Key words: rheumatoid arthritis, depression.

Introduction

RA is a chronic inflammatory disease that results in recurrent joint pain, swelling and deformities. Depression is a common co-morbidity in this population, with the prevalence of depression among RA subjects approximately two to three times higher than that in the general population, and independent of socio-demographic determinants [1–3]. Complications associated with depression in RA patients include an increased risk of work disability, mortality and myocardial infarction [4–6]. Further, depression increases direct medical costs by ~7.2% ($12 225 vs $11 404) per patient per year in those with RA [7]. Beyond the increases in risk for poor health, and associated greater health care costs, depression interferes with daily functioning and worsens quality of life.

Depression could influence RA disease activity, medication duration and treatment outcomes, and thus the course of RA disease progression. Among RA patients, depression is often under-recognized and not managed appropriately [8–10]. In the general population, 30–50% of depression patients do not receive adequate treatment, despite clinical recommendations to do so [11]. This is particularly important in RA patients due to the potential physical and psychological benefits [8, 9, 12]. However, the presence of depression coexisting with a chronic medical condition makes the management of both conditions challenging and may result in poorer clinical response to standard therapies [13, 14].

The mechanisms and interactions between depression and RA disease progression are largely unclear, but it has been suggested that the causal pathways are bidirectional, with depression impacting RA disease activity and...
vice versa [8, 9, 12]. There are conceivable explanations for a bidirectional relationship, which include biological, psychological and behavioural processes [12, 15–17]. Depression is characterized by both repetitive negative thoughts and activation of the immune system [17, 18]. Thus, negative cognitions could influence how RA patients perceive their symptoms, or depression and RA may share pro-inflammatory cytokine mechanisms [19–22]. Depression also impacts physical behaviour and may cause decreases in movement, a deconditioning of the body, loss of natural endorphins and increased pain [23–29]. Many cross-sectional analyses have found depression to be associated with pain, functional status, disease biomarkers, disease duration and RA treatment [30–35]. However, due to their inherent limitations, temporality cannot be assessed, and they provide no evidence regarding directionality or causation. Therefore, an evaluation of studies that specifically assess the impact of depression on RA disease outcomes over time is necessary.

To address the gaps in the current literature, we performed a systematic review to ascertain whether depression is temporally associated with prospective changes in RA disease activity, treatment persistency and clinical outcomes. Given the dramatic increase in the use of biologic DMARDs, upwards of 41% in some populations by 2006, the research literature retrieved was restricted to this biologic era encompassing 1998 to the present day [36]. Consequently, our derived findings are relevant to current RA patient populations.

Methods

We conducted a systematic review of all the accessible medical literature through 31 August 2011 that examined the temporal association of depression with RA disease outcomes, the moderating or mediating effects of depression on clinical treatments, and its relation to RA treatment persistency.

Literature search

The following electronic databases were searched: PubMed, Medline, CINAHL, ISI Web of Science and the Cochrane Central Register of Controlled Trials. The medical subject heading (MeSH) terms used were: depression, rheumatoid arthritis, and depression and rheumatoid arthritis. MeSH terms were combined with certain keywords: disease, health, treatment, outcome and symptoms. The specific search strings used were: depression and rheumatoid arthritis and disease; and depression and rheumatoid arthritis and health; and depression and rheumatoid arthritis and treatment; and depression and rheumatoid arthritis and outcome; depression and rheumatoid arthritis and symptoms. Manual searches of reference lists of the full-text articles that were reviewed were also conducted.

Selection criteria

Articles had to meet the following criteria: (i) human subjects; (ii) diagnosed RA or a subset of RA patients analysed as a unique study sample; (iii) studies with longitudinal outcome measures in relation to depression; (iv) specific measurement and analysis of depression in relation to downstream RA disease outcomes because due to the possible bidirectional effects studies evaluating both at the same measurement time point cannot provide estimates of temporal associations, or studies where depression served as a mediator or moderator of RA treatment; (v) outcome assessments that constituted a relevant RA disease outcome (e.g. swollen joint counts, DMARD discontinuation); (vi) study data derived from after 1 January 1998 or an interval that overlapped this period; and (vii) longitudinal assessment for at least > 6 weeks, which was chosen because it was the approximate time period believed to be necessary for any received treatment to take effect. Exclusion criteria were the following: (i) publication before 1 January 1998; (ii) non-English language publication; and (iii) meta-analyses, review articles, case studies, case series and opinion pieces/editorials.

Definitions

Study populations comprised patients with physician-diagnosed RA. Depression was defined using a broad framework and did not imply a clinical major depressive disorder diagnosis. Acceptable measures included physician diagnosis, assessment based on Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria, validated measurement scales and patient self-report. Study outcome variables encompassed three categories: disease activity, treatment persistence and response to treatment. Pertinent outcomes included the following: clinical disease activity index, 28-joint DAS (DAS28), physician global disease activity using a visual analogue scale (VAS), patient global disease activity VAS, patient pain VAS, HAQ, tender and swollen joint counts (TJCs and SJCs, respectively), and measures indicative of treatment persistency based on medical record review (e.g. DMARD discontinuation).

Data abstraction and quality rating

Articles were first reviewed using their titles and abstracts to determine whether the study included (i) a patient population with diagnosed RA, (ii) longitudinal measures and (iii) measurement and analysis of depression that allowed for a temporal interpretation regarding depression and prospective RA outcomes. Full-text articles were retrieved for the studies meeting these criteria and further reviewed by two study investigators (A.M.R. and G.W.R.). A data abstraction form that was developed and pilot tested prior to data collection was used to gather information, and articles not meeting the more specific inclusion criteria were subsequently excluded. Dual data abstraction was performed in pairs by the primary investigators (A.M.R. and L.R.H. or A.M.R. and G.W.R.) for the included articles. The 26-item Downs and Black quality rating scale was used to evaluate studies included in the review [37]. Pairs of study investigators (A.M.R. and L.R.H. or A.M.R. and G.W.R.) conducted the quality ratings. The results from the data abstractions and quality ratings were
then compared and disagreements were discussed among the reviewers until a consensus was reached.

**Analyses**
The studies were examined regarding their general descriptive characteristics and data such as sample size, outcomes and other related information. The articles were then evaluated for the specific methods utilized, and a simple evaluation of the observed effects regarding depression’s association with RA disease activity or treatment was performed. Quantitative analyses were not possible due to the vast heterogeneity of study designs and effect estimates.

**Results**

**Electronic database search**
The search strategy identified 939 potentially relevant articles. The results of the literature search are illustrated in Fig. 1. Based on an assessment of the article abstracts for inclusion and exclusion criteria, 39 (4.2%) full-text publications were selected for further review. There were subsequently 32 more exclusions: 1 due to the authors not discriminating among the RA and OA sub-groups during analysis; 1 because the study population constituted a combination of RA patients and patients with undifferentiated early inflammatory arthritis; 2 included an intervention considered to influence both depression and RA; 9 with analyses that left no way to discern directionality; 10 with unrelated outcomes that did not constitute a measure of RA disease activity, severity, functional status or treatment persistence; 2 with a follow-up time period of <6 weeks; and 7 with data collection prior to 1998; leaving a final sample of 7 articles [38–44]. Hand-searching techniques based on the review of references did not yield additional publications.

**Study characteristics**
A total of seven publications were included in the review (Table 1) [38–44]. The patient populations constituted mostly middle-aged and elderly women in the USA or Europe. Study designs were the following: five prospective cohorts, an experimental study with a randomized treatment allocation and a post hoc analysis of pooled clinical trial data, with sample sizes ranging from 45 to 389.

Fig. 1 Flow diagram of article selection process.
TABLE 1 General descriptive data and characteristics for the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>n</th>
<th>Percentage female</th>
<th>Mean age</th>
<th>Study location</th>
<th>Depression type</th>
<th>Depression measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zautra and Smith [38]</td>
<td>2001</td>
<td>Prospective cohort</td>
<td>87</td>
<td>100</td>
<td>62.3</td>
<td>USA</td>
<td>Current</td>
<td>MHI—nine items</td>
</tr>
<tr>
<td>Zautra et al. [39]</td>
<td>2004</td>
<td>Prospective cohort</td>
<td>45</td>
<td>100</td>
<td>61.2</td>
<td>USA</td>
<td>Current</td>
<td>MHI—nine items</td>
</tr>
<tr>
<td>Wong and Mulherin [40]</td>
<td>2007</td>
<td>Prospective cohort</td>
<td>68</td>
<td>60.30</td>
<td>55.8</td>
<td>UK</td>
<td>Current</td>
<td>BDI</td>
</tr>
<tr>
<td>Zautra et al. [41]</td>
<td>2008</td>
<td>Experimental</td>
<td>144</td>
<td>67.40</td>
<td>54.3</td>
<td>USA</td>
<td>Past</td>
<td>Clinical diagnosis by DSM-IV criteria</td>
</tr>
<tr>
<td>Hider et al. [42]</td>
<td>2009</td>
<td>Prospective cohort</td>
<td>159</td>
<td>72</td>
<td>56.4</td>
<td>UK</td>
<td>Current</td>
<td>HADS</td>
</tr>
<tr>
<td>Mattey et al. [43]</td>
<td>2010</td>
<td>Prospective cohort</td>
<td>162</td>
<td>70</td>
<td>57 a</td>
<td>UK</td>
<td>Current</td>
<td>HADS</td>
</tr>
<tr>
<td>Kekow et al. [44]</td>
<td>2011</td>
<td>Quasi experimental</td>
<td>389</td>
<td>73.00</td>
<td>51.7</td>
<td>Germany</td>
<td>Current</td>
<td>HADS</td>
</tr>
</tbody>
</table>

*Indicates that age is a median value.

The depression measurement methodologies utilized differed as well. The general methods of assessment included scaled measurement instruments and clinical evaluation using DSM-IV criteria. The specific instruments used were the Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS) and Mental Health Inventory (MHI) depression subscale. In the studies using a scaled measurement instrument, the investigators evaluated patients’ current depression. Of these studies, four defined depression via a designated cut-point, while two analysed the raw instrument score as a continuous variable [38–40, 42–44]. The randomized controlled trial (RCT) used a cut-point based on the patients’ number of past depressive episodes [41].

Quality assessment

Quality ratings ranged from 15 to 22, with a median score of 16, consistent with minimal to moderate methodological quality. The common themes that emerged regarding items resulting in lower scores were sampling and recruitment strategies, inadequate adjustment for confounders, a lack of information on losses to follow-up, randomization and measurement blinding. No studies meeting all of the inclusion and exclusion criteria of this systematic review were excluded due to quality scores.

RA disease activity

Disease activity was evaluated in two studies, which followed women with RA on low-dose (≤10 mg weekly) MTX (≤10 mg weekly) and low-dose prednisone (≤7.5 mg daily), and examined how depression influenced longitudinal RA disease activity as well as its moderating effect on stress (Table 2) [38, 39]. One found baseline depression scores to be predictive of patient reported pain up to 20 weeks, independent of age and follow-up time [38]. Higher baseline depression was predictive of future increases in pain. Also, depression was a moderator of stress and its impact on pain, as it augmented the corresponding increases in pain associated with greater levels of stress. In a subset from the same cohort, subjects’ level of depression was categorized into high or low groupings using the mean score of two time points and the observed median value as a cut-off [39]. Depression was a significant moderator of stress, with high depression correlating to a greater effect of stress on disease activity, as measured by the physician global assessment VAS and TJC scores. However, depression did not moderate stress-associated changes in CD4, CD8 and CD25 T cells or IL-6.

RA treatment persistence

Two articles investigated RA treatment persistency, which was identified based on medical record review, as a function of baseline depression in patients initiating a non-biologic or biologic DMARD (Table 3) [40, 43]. The study outcomes included treatment discontinuation for any reason as well as inefficacy. Wong and Mulherin [40] found no association between baseline depression and DMARD discontinuation for any reason at 1-year follow-up in adjusted analyses. Conversely, in univariate analyses, Mattey et al. [43] found a significant positive association (HR = 1.68; CI 1.08, 2.60) between baseline depression and the discontinuation of an anti-TNF biologic DMARD for any reason. The effect of the association was stronger (HR = 1.86; CI 1.01, 3.43) when restricted to discontinuations due to inefficacy.

Response to RA treatment

Three studies assessed how depression moderated treatment outcomes among patients initiating MTX, combination therapy MTX and etanercept, any of the anti-TNFs, cognitive behavioural therapy (CBT) and mindfulness meditation/emotion regulation therapy (MM/ERT) (Table 4) [41, 42, 44]. One examined the moderating effect of depression on disease activity as measured using the DAS28 among patients initiating anti-TNF therapy [42]. While baseline depression did not influence DAS28 responses at 1 year, those with persistent depression (defined as depression at baseline and 3 months...
### TABLE 2 Temporal associations between depression and RA disease activity in longitudinal analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>Depression measurement</th>
<th>Moderating association</th>
<th>Relevant outcomes</th>
<th>Primary statistical methods</th>
<th>Significant unadjusted associations</th>
<th>Significant adjusted associations</th>
<th>Effect direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zautra and Smith [38]</td>
<td>MHI—nine items</td>
<td>No</td>
<td>VAS pain</td>
<td>Random effects models</td>
<td>NA</td>
<td>Yes</td>
<td>Baseline depression increased pain at 12-20 weeks follow-up</td>
</tr>
<tr>
<td></td>
<td>MHI—nine items</td>
<td>Yes—stress</td>
<td>VAS pain</td>
<td>Random-effects models</td>
<td>NA</td>
<td>Yes</td>
<td>Baseline depression increased the effect of stress at 12-20 weeks follow-up</td>
</tr>
<tr>
<td></td>
<td>MHI—nine items</td>
<td>Yes—stress</td>
<td>Physician global VAS</td>
<td>Repeated-measures ANOVA</td>
<td>NA</td>
<td>Yes</td>
<td>Categorized depression status increased the effect of stress at up to 20 weeks follow-up</td>
</tr>
<tr>
<td></td>
<td>MHI—nine items</td>
<td>Yes—stress</td>
<td>TJC</td>
<td>Repeated-measures ANOVA</td>
<td>NA</td>
<td>Yes</td>
<td>Categorized depression status increased the effect of stress at up to 20 weeks follow-up</td>
</tr>
<tr>
<td></td>
<td>MHI—nine items</td>
<td>Yes—stress</td>
<td>CD4, CD8, CD25 T cells</td>
<td>Repeated-measures ANOVA</td>
<td>NA</td>
<td>No</td>
<td>Categorized depression status increased the effect of stress at up to 20 weeks follow-up</td>
</tr>
<tr>
<td></td>
<td>MHI—nine items</td>
<td>Yes—stress</td>
<td>IL-6</td>
<td>Repeated-measures ANOVA</td>
<td>NA</td>
<td>No</td>
<td>Categorized depression status increased the effect of stress at up to 20 weeks follow-up</td>
</tr>
</tbody>
</table>

NA indicates that the specified association was not available in the published manuscript. Bold text indicates a significant association. ANOVA: analysis of variance.

### TABLE 3 Evidence regarding depression and prospective RA treatment persistency

<table>
<thead>
<tr>
<th>Study</th>
<th>Depression measurement</th>
<th>Moderating association</th>
<th>Relevant outcomes</th>
<th>Primary statistical methods</th>
<th>Significant unadjusted associations</th>
<th>Significant adjusted associations</th>
<th>Effect direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong and Mulherin [40]</td>
<td>BDI</td>
<td>No</td>
<td>Any DMARD discontinuation</td>
<td>Logistic regression modeling</td>
<td>NA</td>
<td>No</td>
<td>Baseline depression was not associated with DMARD discontinuation</td>
</tr>
<tr>
<td>Mattey et al. [43]</td>
<td>HADS</td>
<td>No</td>
<td>Anti-TNF biologic discontinuation</td>
<td>Cox regression</td>
<td>Yes</td>
<td>NA</td>
<td>Baseline depression increased the risk for anti-TNF biologic DMARD discontinuation</td>
</tr>
</tbody>
</table>

NA indicates that the specified association was not available in the published manuscript. Bold text indicates a significant association. aPoint estimates specific to depression were not given.
### Table 4 Evidence for the moderating effects of depression on RA disease treatment outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Depression measurement</th>
<th>RA treatment</th>
<th>Relevant outcomes</th>
<th>Primary statistical methods</th>
<th>Significant unadjusted associations</th>
<th>Significant adjusted associations</th>
<th>Effect direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zautra et al. [41]</td>
<td>Evaluation by DSM-IV criteria</td>
<td>Non-pharmacotherapies</td>
<td>VAS pain</td>
<td>Random-effects models</td>
<td>No</td>
<td>NA</td>
<td>Past depression decreased the effect of treatment pre- to post-intervention</td>
</tr>
<tr>
<td></td>
<td>Evaluation by DSM-IV criteria</td>
<td>Non-pharmacotherapies</td>
<td>SJC/TJC</td>
<td>Random-effects models</td>
<td>Yes</td>
<td>NA</td>
<td>Past depression decreased the effect of CBT treatment pre- to post-intervention Past depression increased the effect of emotional regulation and mindfulness meditation treatment pre- to post-intervention</td>
</tr>
<tr>
<td>Hider et al. [42]</td>
<td>Evaluation by DSM-IV criteria</td>
<td>Non-pharmacotherapies</td>
<td>IL-6</td>
<td>Random-effects models</td>
<td>Yes</td>
<td>NA</td>
<td>Past depression decreased the effect of treatment pre- to post-intervention</td>
</tr>
<tr>
<td></td>
<td>HADS</td>
<td>Anti-TNF biologic DMARDs</td>
<td>DAS28</td>
<td>Non-parametric statistics</td>
<td>(A) No  (B) Yes</td>
<td>NA</td>
<td>(A) Baseline depression decreased the effect of treatment at 3 months follow-up, but increased the effect at 1 year follow-up (B) Persistent depression decreased the effect of treatment at 3 months follow-up</td>
</tr>
<tr>
<td>Kekow et al. [44]</td>
<td>HADS</td>
<td>MTX, or MTX and ETN</td>
<td>DAS28</td>
<td>Simple parametric statistics</td>
<td>Yes</td>
<td>NA</td>
<td>Baseline depression decreased the effect of treatment at 2 years follow-up</td>
</tr>
<tr>
<td></td>
<td>HADS</td>
<td>MTX, or MTX and ETN</td>
<td>ACR 20, 50, 70</td>
<td>Simple parametric statistics</td>
<td>Yes</td>
<td>NA</td>
<td>Baseline depression decreased the effect of treatment at 2 years follow-up</td>
</tr>
<tr>
<td></td>
<td>HADS</td>
<td>MTX, or MTX and ETN</td>
<td>HAQ-DI</td>
<td>Simple parametric statistics, ANCOVA</td>
<td>Yes  (A) No  (B) No</td>
<td>Baseline depression decreased the effect of treatment at 2 years follow-up (A, B) Baseline depression decreased the effect of treatment at 2 years follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HADS</td>
<td>MTX, or MTX and ETN</td>
<td>VAS pain</td>
<td>Simple parametric statistics, ANCOVA</td>
<td>Yes  (A) No  (B) Yes</td>
<td>Baseline depression decreased the effect of treatment at 2 years follow-up (A) Baseline depression decreased the effect of treatment at 2 years follow-up in those achieving remission (B) Baseline depression decreased the effect of treatment at 2 years follow-up in those not achieving remission</td>
<td></td>
</tr>
</tbody>
</table>

NA indicates that the specified association was not available in the published manuscript. Bold text indicates a significant association. aDue to small sizes comparisons were based on having >1 previous episode of clinical depression. bComparator depression groups were stratified by clinical remission status at 2 years follow-up. ANCOVA: analysis of covariance; ETN: etanercept.
follow-up) had significantly smaller decreases in DAS28 scores at follow-up when compared with controls (1.7 vs 2.2, respectively). Kekow et al. [44] performed a post hoc analysis of pooled RCT data of RA patients initiating MTX or MTX plus etanercept. They found patients classified with depression at baseline when compared with those without to have a significantly lower probability of achieving clinical remission and low disease activity as measured by the DAS28 (42.4% vs 56.3% and 56.3% vs 69.3%, respectively), as well as an ACR20, 50 or 70 response, functional improvement based on the Health Assessment Questionnaire Disability Index (HAQ-DI) and pain improvement based on the patient pain VAS, at 2 years follow-up in unadjusted analyses. When the authors examined the impact of depression on HAQ-DI and VAS pain outcomes stratified by remission status, only VAS pain scores were influenced by depression in those not achieving remission in adjusted analyses.

One RCT evaluated the moderating influence of past depression on response to non-pharmacological interventions including: (i) CBT, (ii) MM/ERT and (iii) an education only (EO) control group [41]. Recurrent depression did significantly moderate changes in TJC and SJC scores, overall and by treatment grouping. Compared with the CBT and EO treatments, the MM/ERT intervention resulted in greater decreases in TJC and SJC scores in patients with prior depression. Conversely, counts actually increased in those receiving CBT among those with prior depression. However, among patients without prior depression the MM/ERT intervention was less efficacious compared with the other intervention groups, and patients’ joint counts increased. In contrast, the CBT treatment and EO control groups had decreases in their TJC and SJC scores. Additionally, patients with prior depression had significantly higher pre- and post-IL-6 levels that showed no moderating effects by intervention grouping.

**Discussion**

This review demonstrates that there is scant research literature examining the temporal relationship between depression and RA disease activity, medication persistency and response to therapy. Only seven publications met all the specific inclusion and exclusion criteria, and they were scored low to moderate in terms of methodological quality [38–44]. Several studies found significant associations indicating that pre-existing depression may significantly worsen RA symptoms and reduce medication persistency as well as diminish the efficacy of pharmacological and non-pharmacological therapies [38, 39, 41–44]. Yet, the results within some studies were somewhat conflicting, where depression was not always consistently significantly associated with the outcomes of interest in a particular study [41, 44].

When assessing disease activity, depression was predictive of elevations in future pain, moderated stress-associated changes in pain, TJC and physician global VAS scores [38, 39]. Similar findings regarding pain have been observed in studies using patients with early inflammatory arthritis and PsA, yet these studies found no temporal influence of depression on disease activity as measured using SJC scores [45, 46]. It is certainly plausible that depression exacerbates RA disease activity. Evidence intimates that depression is related to preservative cognition, a process of uncontrolled repetitive negative thinking that may act directly on somatic disease and lead to the activation of cell-mediated immunity [17, 18, 20, 21]. Accordingly, depression could have a tangible impact on RA disease activity due to shared cytokine-regulated events [22]. Alternatively, the symptoms of depression can affect patients’ physical behaviour, resulting in decreased movement and reduced engagement in activities of daily living [23, 24]. Behavioural patterns established during periods of depressed mood that lead to reduced physical activity, may result in a deconditioning of the body, and loss of natural endorphins, which could increase musculoskeletal pain [25–29]. Of note, no physician assessed swollen joint counts or standard laboratory-derived measures of disease activity were used, and the analyses focused mostly on patient-reported metrics of disease activity.

The two included studies examining depression and treatment persistence yielded different findings, and only one showed that depression significantly influenced treatment duration [43]. The observed difference may have been due to inadequate adjustment in the analysis. Medication persistence is complex and influenced by a variety of factors, including income (i.e. ability to pay for a medication), knowledge and beliefs concerning the perceived harms and benefits of therapy, adverse events and the patient-provider relationship. Further, depression is likely to be associated with some of these factors, such as socio-economic status, which influences income and likely treatment persistence [47].

The research examining depression and RA treatment outcomes suggests depression may decrease short-term and long-term DMARD efficacy, as measured by the DAS28 and patient-reported outcomes [42, 44]. Thus, subjects with chronic depression may not derive immediate benefit from treatment, and minimal levels of depression may affect long-term patient outcomes. If depression increases the risk for medication discontinuation or poor DMARD response due to a substantive impact on pain or inflammation, then it may be an important factor contributing to therapeutic inefficacy. However, these results may be purely a response tendency, where participants choose the more negative options available concerning patient-reported measures of disease activity because of the preservative cognitions that are associated with depression. Yet, it should be noted that not all treatments were adversely affected by the presence of depression. Certain non-pharmacological treatments (e.g. ERT/MM) performed well in RA patients with prior depression, and given their impact such approaches could be integrated with medication management [41].

This systematic review has several limitations. Foremost, very few studies were included in this review, as the topic has not been well explored in the literature. The different depression measures may hinder any interpretations of the observed associations. Further, only
English-language articles were reviewed, grey literature, not in the available electronic databases, may have been missed, and a quantitative meta-analysis was not possible. There were also general limitations associated with the available research. Most studies did not outline a priori objectives to specifically evaluate how depression influenced future RA outcomes. Consequently, there were limited measures and analyses performed examining this temporal relationship. The use of restricted and convenience study samples may have resulted in selection bias and reduced generalizability, respectively. Also, sample sizes were often small, thus lacking statistical power, particularly regarding the moderating effects of depression, and when no signals were identified, it may have been due to the lack of power. Finally, there was generally inadequate adjustment for confounders, and the observed results could have been due to other factors rather than depression.

The existing data suggest that depression impacts RA patients in several ways. Depression may worsen pain and disease activity; though it is unclear whether this is via a response shift created by repetitive negative thinking, immunologically mediated mechanisms that affect inflammation or a combination of psychological, behavioural and biological factors that impact the sensation of pain. It is possible that such determinants influence RA treatment persistence; albeit, the results were discordant. In contrast, the presence of depression in all studies evaluated generally decreased patient response to pharmacological treatment, and in some instances, non-pharmacological interventions. Given the limited evidence currently available, much more research is needed.

Conclusions
Although understanding the mechanisms underlying these associations is important, future studies must first discern how depression influences the diverse metrics that encompass RA disease activity measurement. Determining how depression is temporally associated with both subjective and objective markers of RA disease activity will aid in identifying any shared causal underpinnings that connect these two chronic conditions and provide an overarching framework for all subsequent investigations into the specific mediating factors. Also, research that examines how depression moderates pharmacological treatment in larger heterogeneous observational cohorts is necessary, as it could be used to help develop recommendations for practising rheumatologists.

Disclosure statement: G.W.R. works as the lead biostatistician and consultant on the Consortium of Rheumatology Researchers of North American (CORRONA) National Arthritis Registry. L.R.H. is a paid consultant to CORRONA. The other author has declared no conflicts of interest.

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