Published in final edited form as:

Clin Ther. 2016 July ; 38(7): 1759–1772.e3. doi:10.1016/j.clinthera.2016.06.007.

A Prospective Evaluation of the Effects of Prevalent Depressive Symptoms on Disease Activity in Rheumatoid Arthritis Patients Treated with Biologic Response Modifiers

Alan M. Rathbun, PhD, MPH* [Postdoctoral Research Fellow],

University of Maryland School of Medicine, 685 West Baltimore Street, Baltimore, MD 21201

Leslie R. Harrold, MD, MPH [Associate Professor of Orthopedics], and

University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655;

leslie.harrold@umassmed.edu

George W. Reed, PhD [Professor of Medicine]

University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655;

George.reed@umassmed.edu

Abstract

Purpose—Depressive symptoms are common in rheumatoid arthritis (RA) and may impact disease activity and treatment outcomes. The objective was to determine if prevalent depressive symptoms modify biologic treatment response through their effect on RA disease activity.

Methods—RA patients with depressive symptoms, initiating biologic treatment, were identified from an American RA registry sample. Depressed patients were compared to controls, patients without reports of depressive symptoms at, or prior to, initiating therapy, regarding CDAI remission and low disease activity (LDA), and the changes in the component measures that comprise this scale at 6 and 12 months follow-up. Inverse probability weighting was used to account for differences in baseline disease severity, concomitant treatment characteristics, and other possible confounders. Logistic and linear regression models estimated differences in response rates and changes in component disease activity measures.

Findings—Depressive symptoms were associated with a decreased likelihood of CDAI remission at 6 months (OR=0.43; 95% CI: 0.19, 0.96) but not 12 months (OR=0.83; 95% CI: 0.43, 1.60), and there was no effect on CDAI LDA. Adjusted core component measurement changes

* **Corresponding Author:** Alan M. Rathbun, Department of Epidemiology and Public Health, University of Maryland School of Medicine, Howard Hall Suite 200, 660 W. Redwood Street, Baltimore, MD 21201. Phone: (410) 706-5151; fax: (410) 706-4433; arathbun@epi.umaryland.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

CONFLICTS OF INTERESTS

Dr. Leslie R. Harrold is Senior Medical Director of Pharmacoepidemiology and Outcomes Research at CORRONA, LLC and has received research grants to her institution from CORRONA. Dr. George W. Reed is Chief Statistical Officer of the CORRONA registry and holds stock options in CORRONA, LLC. Dr. Alan M. Rathbun has no conflicts of interests to declare. The study sponsors had no role in the design of the study, analysis and interpretation of data; the writing of the manuscript; and the decision to submit the manuscript for publication.

showed smaller decreases in global assessment ratings in patients with depressive symptoms, yet these associations were not statistically significant.

Implications—Poorer treatment outcomes among RA patients with depressive symptoms may be a result of higher baseline disease severity. Adjusted estimates indicated symptoms of depression only impacted remission at 6 months follow-up through patient and physician global assessments. Thus, any impact of depressive symptomology during biologic treatment might not due to a definitive impact on joint swelling and tenderness.

Keywords

Depression; Rheumatoid arthritis; Epidemiology; Outcomes; Therapeutics

INTRODUCTION

Medical comorbidity is a significant problem in rheumatoid arthritis (RA) patients, the most prevalent autoimmune inflammatory arthritic disorder in the United States, and evidence suggests it is an important clinical component that rheumatologists should be attentive to when utilizing treat-to-target approaches (1,2). Psychiatric disorders in RA are common, particularly depression, with an estimated point prevalence of 16.8% (10%-23%) that is significantly greater compared to the general population (3,4). Guidelines recommend that physicians be aware of depression in those suffering from chronic physical illness, yet the condition is under-recognized in the primary care and specialty practice settings (5-7). The presence of depression in RA may also influence disease activity, and therefore, outcomes of therapeutic treatment (8).

Biologic disease modifying anti-rheumatic drugs (DMARDs) revolutionized RA care by increasing within-patient response and providing treatment options for patients not responding to conventional treatments. The use of these medications has been estimated to have tripled in seven years from 13% to 41% (9). Despite such improvements, co-occurring depression in chronic physical disease causes medical management to become difficult, and more than 20% of patients starting biologic therapy suffer from this comorbidity (10,11). Researchers have posited unimodal treatment approaches lead to improvements in the two conditions simultaneously; however, interventional study data indicates that depression results in poorer response for both disorders when either is treated individually (10,12).

Cross-sectional studies have demonstrated the association between depression and disease activity among RA patients treated with biologics (13-17), but few have examined how depression prospectively affects biologic treatment response (18-20). Post-hoc analyses of clinical trial data suggest a significantly lower likelihood of DAS28 remission and low disease activity (LDA) in patients with depressive symptoms receiving mono- and combination therapy for RA (19,20). Observational study findings have also shown lower DAS28 response rates among treated individuals initiating an anti-TNF with persistent depressive symptoms (18). Although, these studies did not assess how component RA disease activity measures change following biologic treatment (18-20) and used restricted samples lacking generalizability (19,20). Depression may affect biologic treatment response,

but it is unclear if this is due to an effect on inflammation or subjective global assessments of disease activity (8,14,15).

Research on biologic DMARDs has been named as a top priority by the Institutes of Medicine, yet few studies have rigorously investigated how this highly prevalent comorbidity affects therapeutic response (3,8,21). As prevalent depressive symptoms have been demonstrated to impact the trajectory of RA disease activity, our objective was to evaluate the moderating effects of prevalent depressive symptoms on response to biologic agents using a large national RA registry (22).

METHODS

Study Data

The Consortium of Rheumatology Researchers of North America is a national prospective cohort of American RA patients. Patients are enrolled at participating academic and community rheumatology clinics by their treating CORRONA physician, and more comprehensive information regarding the database operation and funding mechanisms has been published elsewhere (23). For this study, approvals for data collection and analyses were obtained from a central institutional review board, the New England Institutional Review Board, with respect to private practicing sites participating in CORRONA. Institutional review boards for CORRONA sites affiliated with academic medical centers (<20%) were the local Institutional Review Boards of record. All patients approved for enrollment provided informed consent prior to entry into the study. Information is collected using surveys administered to both patients and their corresponding rheumatologists at routine clinical encounters that generally occur every 3 to 6 months (23). Surveys gather data on demographics, behavioral characteristics, disease activity and severity, medical comorbidity, and extensive information related to DMARD medication prescriptions.

Depression Measures

CORRONA registry data have patient- and rheumatologist-reported depression measures collected using single-item assessments from a comorbidity inventory list (7). However, estimated depression rates using the rheumatologist-reported measures are much lower than general population estimates, which is indicative of the under-recognition and –reporting of this comorbidity by practicing rheumatologists (7). In contrast, patient-reported depression rates were reflective of the trends that would be expected based on prior research (7). Thus, the patient-reported depression measures were used to identify and assess prevalent depressive symptoms in the current study. Patient surveys capture data on prior depression at enrollment and information during follow-up regarding medical comorbidities that occurred since their last visit. Enrollment forms instruct patients to, “Please fill a ‘NO’ or ‘YES’ circle for each of the following conditions you have EVER had.” Follow-up surveys instruct study participants to report any “Medical condition or symptom you have had SINCE YOU LAST FILLED OUT THIS FORM,” which contains an item for “Depression.”

These measures were used to assign patient's depressive symptom status at their assigned index date; although, they were not intended to characterize major depressive disorder as

diagnosed using DSM criteria. Nonetheless, self-reported depressive symptoms, which include questions about being “depressed,” are routinely used to evaluate depression in clinical practice and have been developed and validated in patients with chronic physical disease (24-26). Moreover, patient-reported comorbidity has been well validated and is more reliable than physician-reported information, particularly for depression (6,7,27,28), and several studies have used these measures to assess the impact of depression in RA patients (7,20,22,29). Given the burden of longer screening instruments in busy practice sites, these measures are feasible alternatives that provide valuable clinical information (24,30).

Patient Selection

RA patients (N=33,743) enrolled between October 2001 to August 2012 were analyzed, which included participants (N=4,592) initiating their first observed biologic agent during follow-up (**Figure 1**). Enrollment visits were not used because only measures of lifetime prevalent depression are collected rather than recently occurring depressive symptoms. Patients without disease activity and covariate data (n=1,644) and follow-up visits after treatment initiation (n=397) were excluded. A history of depression was defined as a self-reported lifetime prevalence at enrollment or presence of depressive symptoms during follow-up before starting therapy. Patients with prevalent depressive symptoms (n=300) had (1) self-reported symptomology at the visit where biologic treatment initiation was assigned and (2) a history of symptoms of depression. Controls (n=1,520) had no self-reported depressive symptoms at, or prior to, treatment initiation. The selected patients included 1,520 controls and 300 patients with prevalent depressive symptoms, and analytic samples were further refined based on level of disease activity at treatment initiation.

Response Variables

Remission and LDA were defined using the clinical disease activity index (CDAI). The CDAI is a summary score (0-76) calculated from the swollen joint count (SJC) based on 28 counts, tender joint count (TJC) based on 28 counts, patient global assessment of disease activity (PGA; visual analogues scale (VAS) 0-10 cm)), and physician global assessment of disease activity (EGA; VAS 0-10 cm) (31). CDAI remission and LDA are defined using cut point values of < 2.8 and < 10, respectively. In accordance with recent recommendations, the disaggregated values (SJC, TJC, PGA, and EGA) were assessed as the change in each continuous value from treatment initiation to follow-up (14). The CDAI was used as the primary outcome variable because other composite measures that incorporate acute phase reactants (e.g., 28 joint count disease activity score [DAS28]) have much higher rates of missing data (50%) and their use would have resulted in a substantial loss of statistical power. Moreover, the CDAI has equivalent measurement properties compared to the DAS28 and was characterized as having excellent validity and responsiveness (32). Response to therapy was assessed at 6 and 12 months (+/- 2 months) follow-up. Patients that discontinued therapy had their outcomes imputed as non-response, and the last available observation was carried forward when assessing component measures (33). When assessing remission, patients in remission at initiation were excluded, and similarly, when LDA was the outcome of interest, only patients in moderate-to-severe at baseline were included.

Potential Confounders

Differences in key covariates that could influence response and were associated with patients' depression status were of concern, and confounders were measured from the index dates where treatment initiation was assigned.

Sociodemographic factors included self-reported measures of gender, age, marital status, race, ethnicity, achieved education, employment, and health insurance. Patients' age at enrollment was modeled as a two-piece linear spline due to a non-linear relationship with the likelihood of reporting concurrent depressive symptoms. Marital status was captured as five categories: single, married/partnered, widowed, and divorced/separated. Ethnicity and Race, reported as separate variables, were combined into a single measure: White, Black, Asian, Hispanic, and Other. Level of attained education was characterized using three groups: primary, high school, and college/university; and employment status was collected as one of six groups: full time, part time, unemployed, student, disabled and retired.

Clinical and behavioral attributes were exercise, alcohol use, smoking, disease duration, body mass index (BMI), and comorbidity. Exercise habits were assessed using five groupings: not at all, 1-2 times per week, 3-4 times per week, 5-6 times per week, and daily. Previous alcohol and smoking exposure were measured as discrete (ever vs. never) binary variables. Reports of prior and current medical conditions from either patients or rheumatologists were used to create a validated composite comorbidity index and included the following: myocardial infarction, stroke, hypertension, other cardiovascular disorders, diabetes mellitus, pulmonary disease, cancer, peptic ulcer, other gastrointestinal disorders, and fractures (34).

Concomitant treatment characteristics included biologic history, biologic class, combination therapy with a non-biologic DMARD, prednisone, and number of prior biologics. Biologic history (experienced vs. naïve) was the reported utilization of any biologic DMARD prior to the index time point, and medication type was characterized using two groups: TNF and non-TNF. Combination therapy was defined as the additional utilization of a non-biologic DMARD (Leflunomide, Sulfasalazine, Azathioprine, Methotrexate, *Hydroxychloroquine*, *Minocycline*, Auranofin, Penicillamine, and Cyclosporin) at treatment initiation. Concomitant prednisone use at treatment initiation was also noted. Number of prior biologic therapies was calculated based on the previous exposure to any of the nine commercially available therapies and truncated at three because of small sample sizes in the higher strata.

Disease severity exhibits strong intra-individual clustering, and baseline values are the strongest predictor of treatment response (35). Without accounting for baseline disease activity, any relationship between depressive symptoms and treatment response may be due to residual confounding. Specifically, depressed patients may have poorer treatment outcomes because they have greater baseline disease severity, rather than depressive symptoms affecting response through a substantive impact on RA disease activity. Therefore, baseline continuous outcome values (i.e., CDAI) from the assigned index dates were considered possible confounders; in addition to patients' pain and functional status, measured using self-reported pain (VAS 0-10 cm) and the modified health assessment questionnaire (mHAQ), which was converted to HAQ values (36).

Inverse Probability Weighting

Inverse probability weighting (IPW) was used to account for possible confounders (37). IPW is implemented in the propensity score (PS) context to account for differences in the probability of exposure between two comparison groups. The exposed and unexposed participants are weighted to represent the overall study sample and can be directly compared without multivariable regression adjustment. Rather than modeling the association between observed exposures and observed outcomes, which cannot be interpreted causally, this method models the relationship between exposures and their potential outcomes (37). IPW was chosen for two reasons: (1) it models counterfactual outcomes and (2) composite disease activity, pain, and function are highly correlated. Thus, findings can be interpreted in a potential outcomes framework and collinearity regarding RA disease activity measures cannot directly bias effect estimates.

Logistic regression was used to calculate a propensity score (PS), the probability of prevalent depressive symptoms at treatment initiation, conditional on confounders associated with their presence. Confounders measured at biologic initiation used to calculate the weights were: CDAI, pain, HAQ, sex, age, education, health insurance, employment status, drinking, smoking, exercise, BMI, comorbidity, antidepressant use, biologic history, combination therapy, methotrexate use, prednisone use, and number of prior biologics. Stabilized IPWs for the exposed and unexposed patients were calculated as $P \div PS$ and $(1-P) \div (1-PS)$, respectively, where P corresponds to the overall sample probability of having the observed exposure status (37). Weights were truncated at the 99th percentile to reduce the influence of outlier values on variance estimates (38). This process was replicated separately in the remission and LDA analytic samples at 6 and 12 months.

Statistical Analysis

Patient characteristics were compared between those with and without prevalent depressive symptoms at treatment initiation. Means and standard deviations were estimated for continuous variables, and t-tests and standardized mean differences were used to assess for differences between the groups. For categorical measures, percentages were calculated and chi-square tests and standardized mean differences were used to examine between-group differences. Standardized mean covariate differences ≥ 0.10 were considered evidence for imbalance (39).

Logistic and linear regression was used to examine differences in response (remission and LDA) and changes in the SJC, TJC, PGA, and EGA at 6 and 12 months. Unadjusted odds ratios (OR) were estimated to quantify the probability of remission and LDA, and model based estimates of change for the component values by prevalent depressive symptom status were calculated. Weighted regression models were used to examine adjusted associations that controlled for baseline differences in sociodemographics, RA disease activity, concomitant treatment characteristics, and other clinical factors. The indicator for prevalent depressive symptoms at treatment initiation tested whether the probability of achieving remission and LDA or change in a component measure differed between the depressed and non-depressed. Sensitivity analyses were performed using patients with both a 6- and 12-months follow-up visit. Statistical significance was set at an alpha level of 0.05 for primary

outcome models. All statistical analyses were conducted using Stata (Version 13, Stata Corp, College Station, Texas, USA).

RESULTS

Patient Characteristics

Depressed RA patients initiating biologic treatment who were not in remission at baseline were more likely to be female, younger, and of lower socioeconomic status (**Table 1**). Prevalent depressive symptoms were also associated with prior smoking, less alcohol use, lower physical activity, and greater BMI, comorbidity, and anti-depressant use. Depressed participants were more experienced with biologic medications and had higher rates of prior utilization and prednisone prescriptions (**Table 2**). However, depressive symptoms were associated with a lower likelihood of combination therapy and MTX use. Depressed patients had significantly greater disease severity as measured by the CDAI, TJC, PGA, EGA, pain, and HAQ (**Supplementary Table 1**). Similar trends were observed when restricting to RA patients with both a 6 and 12 months follow-up visit (**data not shown**). The between-group covariate differences were rebalanced in the weighted pseudo population compared to the original sample as shown by the lower standardized mean covariate differences (**Supplementary Figure 1**).

Remission

Those with prevalent symptoms of depression were significantly less likely to achieve remission in unadjusted analyses, and the corresponding ORs were 0.31 [0.18-0.55] at 6 months and 0.55 [0.34-0.88] at 12 months (**Table 3**). Statistical adjustment for potential confounders via probability weighting attenuated the observed point estimates towards the null. The weighted ORs for remission were 0.43 [0.19-0.96] and 0.83 [0.43-1.60], and the 12 months association was no longer statistically significant. Depressed RA patients had comparable changes in their SJC and TJC ratings compared to non-depressed patients but smaller decreases in global assessment ratings (**Table 4**). The differences in global assessment ratings decreased over follow-up for patients, but increased over time among rheumatologists, and the only unadjusted association to reach statistical significance was the difference in EGA changes at 12 months: 14.1 [12.8, 15.4] vs. 10.0 [7.0, 12.9] in the controls and depressed ($P=0.01$), respectively. Weighted estimates showed that depressed patients had slightly larger decreases in their joint counts, and prevalent depressive symptoms were still associated with smaller PGA and EGA decreases. Standardized differences ranging from 0.02 to 0.06 suggested small effect sizes, and adjusted associations were not statistically significant. Restricting to patients with both a 6 and 12 months visit yielded comparable results (**Supplementary Tables 2 and 3**).

Low Disease Activity

Similarly, depressed patients had a lower probability of achieving LDA (**Table 3**), and the corresponding unadjusted ORs of response at 6 and 12 months were 0.54 [0.39, 0.76] and 0.50 [0.34, 0.73]. However, weighting attenuated the effect estimates and differences in response were negligible. Adjusted ORs for LDA comparing the depressed to non-depressed were 0.91 [0.56, 1.47] and 0.87 [0.51, 1.49] at 6 and 12 months, respectively. The unadjusted

estimated changes in component measures suggested smaller decreases across all metrics in those with prevalent depressive symptoms (**Table 5**). Again, only the comparison in EGA changes between depressed and non-depressed patients at 12 months was statistically significant: 12.3 [8.9-15.6] vs. 17.7 [16.1-19.2], respectively ($P=0.004$). Weighted estimates indicated greater SJC and TJC decreases among those with prevalent depressive symptoms, but proportionally equal, smaller changes in their PGA and EGA ratings. However, none of the observed associations were statistically significant, and the standardized differences (0.02-0.06) indicated the associations were small in magnitude. Restricting to those with both follow-up visits yielded comparable results (**Supplementary Table 2 and 4**).

DISCUSSION

This study investigated biologic DMARD treatment in the context of co-occurring prevalent depressive symptoms. Prevalent symptoms of depression at treatment initiation resulted in a significantly lower adjusted probability of remission at 6 months follow-up. However, the moderating effect on remission lessened over time and was not statistically significant at 12 months. Decomposed estimations of constituent measurement changes suggested these effects were related to non-significant, smaller global assessment declines in depressed patients. In contrast, prevalent depressive symptoms did not affect LDA. While depressed patients had smaller decreases in self- and rheumatologist-reported global assessments, there were larger adjusted declines in joint counts among patients in moderate-to-severe disease activity. Findings suggest that prevalent depressive symptoms only affect the most stringent definition of clinical response proximal to treatment initiation and any impact on therapeutic outcomes is not due to a substantive effect on swollen and tender joints.

Prevalent depressive symptoms contiguous to starting biologic therapy were associated with a significantly lower probability of remission at 6 months but not 12 months. Prior research has generally shown similar moderating effects on the probability of DAS28 remission; although, effect estimates more consistent over time (18-20). These studies, however, did not control for baseline differences in RA disease activity (18,19) and prior use of intensive treatment (18-20). Research demonstrating more consistent effects of depressive symptoms on clinical response may be biased with respect to patient selection (40). More specifically, depressive symptoms are likely a consequence of increases in disease activity over time (29), and when present in RA patients, are strongly associated with disease severity in those initiating biologic treatment (13-17). Rather than depressive symptoms having a substantive effect on inflammation and musculoskeletal pain, depressed RA patients may be less likely to respond to therapy because they have more aggressive disease that is inherently more difficult to manage in the clinical setting.

Constituent measurement changes indicated that prevalent depressive symptoms were differentially associated with individual RA disease activity measures. That is, depressed patients had slightly larger adjusted decreases in their SJC and TJC ratings; and conversely, smaller declines in global assessments. The depressive effect was greatest in magnitude for the PGA at 6 months, but larger for the EGA at 12 months, which is in contrast to prior evidence showing a larger impact of depressive symptoms on patient-reported disease activity measures (22,29). These results imply that depressive symptomology was associated

with a greater response as measured using joint counts, and the lower likelihood of remission at 6 months was related to subjective assessments of RA disease activity, particularly the PGA. The attenuated association at 12 months after adjustment indicates that depressed patients were subsequently more likely to achieve remission, which is supported by prior research demonstrating that depression's effect on RA disease activity decreases as time progress (22). Depressive symptoms at treatment initiation that are an aftereffect of increased disease activity could have a time dependent effect on how patients and rheumatologists interpret and perceive disease status during the course treatment (14,15,22,29).

Finding provided no evidence that prevalent symptoms of depression had a detrimental effect on treatment response as defined using LDA. The unadjusted estimates were similar to previous studies assessing depression as a moderator of biologic DMARD treatment; yet, after controlling for possible confounders any differences in LDA response were attenuated to the null (18-20). Prior studies have shown that depressive symptoms do not temporally influence every metric of RA disease activity and are highly correlated with global assessment scales among patients being treated with biologic agents (14,15,22). The CDAI incorporates the crude value of each component measure, and unlike remission, achieving LDA does not require all constituent values to be low (15,31). The cumulative effect of prevalent depressive symptoms on PGA and EGA ratings may be large enough to significantly impact remission, but the lack of an effect on LDA implies this less stringent definition of response is not affected when only subjectively assessed disease activity measures are influenced by depression. Therefore, depression's impact on RA disease activity during biologic treatment may be reflective of patient's mood and its effects on global assessment ratings, rather than a tangible influence on joint swelling and tenderness (8).

There are some limitations to this study. The operationalization of depressive symptoms was not equitable to depression as evaluated using diagnostic methods. Single item depression measures have high sensitivity, but low specificity, and may result in higher rates of false positives (41). CORRONA data lack a validated form of depression measurement, such as diagnostic assessments or depressive symptom scales, and it is not possible to empirically quantify the level of measurement misclassification. Notwithstanding, any misclassification would have only biased the results if it was differential across people with different levels of RA disease activity. As inflammation is key to the etiology of both depression and RA, the smaller effect sizes in the current study compared to prior research could also be related (in part) to the use of the CDAI because it does not incorporate an acute phase reactant. There is also the possibility of confounding from unmeasured factors (e.g., medication adherence) not included in the analysis and time-dependent confounding from time-varying factors that changed after treatment initiation (42,43). Follow-up assessments were not conducted using a stringent protocol as mandated in clinical trials, and there was between-patient variation in the timing of their 6 and 12 months study visits.

However, these potential sources of bias were mitigated through the use of a large, prospective observational cohort that was specifically designed to investigate RA treatment in the era of biologic DMARD treatment. The CORRONA registry collects comprehensive,

relevant information, which permitted robust statistical adjustment for a range of clinical and concomitant treatment characteristics. Moreover, CORRONA RA patients are recruited from community and academic rheumatology practices from across the US; and thus, these data not only have strong internal validity but are also more generalizable than findings from clinical trial samples.

CONCLUSIONS

In summary, prevalent depressive symptoms only impacted the most stringent definition of clinical response proximal to biologic treatment initiation. In contrast to prior work showing stronger and more uniform effects of depression on biologic treatment response, this study demonstrated that depressed patients were only slower to achieve remission because of non-significant effects of depressive symptoms on patient- and rheumatologist-reported global assessments of disease activity (18-20). Our results highlight the importance of considering patients perceptions and interpretations about their illness during rheumatology care, which in this study were shown to influence both self- and externally-rated metrics of disease status (44,45). Previous work has proposed measurement response shift arising from depressed mood as a potential mechanism to explain depression's impact on subjective assessments of disease status, but unlike results of prior research, the effect on global assessments varied in magnitude over time between patients' and providers (8,22). These data imply a more complex relationship between depressed mood, patient's perceptions and beliefs about their illness, and how provider's assessments are influenced by mood disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This study was supported by a training grant from the National Institute on Aging (T32 AG00262) and the Consortium of Rheumatology Researchers of North America (CORRONA). In the last two years AbbVie, Amgen, Genentech, Horizon Pharma, Lilly, Momenta, Novartis, Pfizer, Regeneron, Vertex, and UCB have supported CORRONA through contract subscriptions. AMR performed the statistical analyses, interpreted the data, and drafted the manuscript. All authors read and approved the final version of the manuscript for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ABBREVIATIONS

RA	Rheumatoid arthritis
CDAI	Clinical Disease Activity Index
LDA	Low disease activity
OR	Odds ratio
CI	Confidence Interval
DMARDs	Disease-modifying anti-rheumatic drugs

CORRONA Consortium of Rheumatology Researchers of North America

IRB	Institutional review board
SJC	Swollen joint count
TJC	Tender joint count
PGA	Patient global assessment
EGA	Physician global assessment
VAS	Visual analogue scale
BMI	Body mass index
HAQ	Health assessment questionnaire
IPW	Inverse probability weights
PS	Propensity score
P	Probability

REFERENCES

1. Ranganath VK, Maranian P, Elashoff DA, Woodworth T, Khanna D, Hahn T, et al. Comorbidities are associated with poorer outcomes in community patients with rheumatoid arthritis. *Rheumatology (Oxford)*. Oct; 2013 52(10):1809–1817. [PubMed: 23813577]
2. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum*. Jan; 2008 58(1):15–25. [PubMed: 18163481]
3. Matcham F, Rayner L, Steer S, Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)*. Dec; 2013 52(12):2136–2148. [PubMed: 24003249]
4. Dickens C, McGowan L, Clark-Carter D, Creed F. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. *Psychosom Med*. Jan-Feb;2002 64(1):52–60. [PubMed: 11818586]
5. Pilling S, Anderson I, Goldberg D, Meader N, Taylor C, Two Guideline Development Groups. Depression in adults, including those with a chronic physical health problem: summary of NICE guidance. *BMJ*. Oct 27.2009 339:b4108. [PubMed: 19861376]
6. Nichols GA, Brown JB. Following depression in primary care: do family practice physicians ask about depression at different rates than internal medicine physicians? *Arch Fam Med*. May; 2000 9(5):478–482. [PubMed: 10810955]
7. Rathbun AM, Harrold LR, Reed GW. A description of patient- and rheumatologist-reported depression symptoms in an American rheumatoid arthritis registry population. *Clin Exp Rheumatol*. Jul-Aug;2014 32(4):523–532. [PubMed: 24984165]
8. Rathbun AM, Reed GW, Harrold LR. The temporal relationship between depression and rheumatoid arthritis disease activity, treatment persistence and response: a systematic review. *Rheumatology (Oxford)*. Oct; 2013 52(10):1785–1794. [PubMed: 23236191]
9. DeWitt EM, Lin L, Glick HA, Anstrom KJ, Schulman KA, Reed SD. Pattern and predictors of the initiation of biologic agents for the treatment of rheumatoid arthritis in the United States: an analysis using a large observational data bank. *Clin Ther*. Aug; 2009 31(8):1871–80. discussion 1858. [PubMed: 19808146]

10. Detweiler-Bedell JB, Friedman MA, Leventhal H, Miller IW, Leventhal EA. Integrating co-morbid depression and chronic physical disease management: identifying and resolving failures in self-regulation. *Clin Psychol Rev*. Dec; 2008 28(8):1426–1446. [PubMed: 18848740]
11. Hyrich K, Symmons D, Watson K, Silman A, BSRBR Control Centre Consortium; British Society for Rheumatology Biologics Register. Baseline comorbidity levels in biologic and standard DMARD treated patients with rheumatoid arthritis: results from a national patient register. *Ann Rheum Dis*. Jul; 2006 65(7):895–898. [PubMed: 16339291]
12. Krishnan KR, Delong M, Kraemer H, Carney R, Spiegel D, Gordon C, et al. Comorbidity of depression with other medical diseases in the elderly. *Biol Psychiatry*. Sep 15; 2002 52(6):559–588. [PubMed: 12361669]
13. Cabrera-Marroquin R, Contreras-Yanez I, Alcocer-Castillejos N, Pascual-Ramos V. Major depressive episodes are associated with poor concordance with therapy in rheumatoid arthritis patients: the impact on disease outcomes. *Clin Exp Rheumatol*. Nov-Dec; 2014 32(6):904–913. [PubMed: 25190569]
14. Cordingley L, Prajapati R, Plant D, Maskell D, Morgan C, Ali FR, et al. Impact of psychological factors on subjective disease activity assessments in patients with severe rheumatoid arthritis. *Arthritis care & research*. 2014; 66(6):861–868. [PubMed: 24339425]
15. Inanc N, Yilmaz-Oner S, Can M, Sokka T, Direskeneli H. The role of depression, anxiety, fatigue, and fibromyalgia on the evaluation of the remission status in patients with rheumatoid arthritis. *J Rheumatol*. Sep; 2014 41(9):1755–1760. [PubMed: 25086073]
16. Uguz F, Akman C, Kucuksarac S, Tufekci O. Anti-tumor necrosis factor-alpha therapy is associated with less frequent mood and anxiety disorders in patients with rheumatoid arthritis. *Psychiatry Clin Neurosci*. Feb; 2009 63(1):50–55. [PubMed: 19154212]
17. Wolfe F, Michaud K. Fatigue, rheumatoid arthritis, and anti-tumor necrosis factor therapy: an investigation in 24,831 patients. *J Rheumatol*. Nov; 2004 31(11):2115–2120. [PubMed: 15517621]
18. Hider SL, Tanveer W, Brownfield A, Matthey DL, Packham JC. Depression in RA patients treated with anti-TNF is common and under-recognized in the rheumatology clinic. *Rheumatology (Oxford)*. Sep; 2009 48(9):1152–1154. [PubMed: 19608723]
19. Kekow J, Moots R, Khandker R, Melin J, Freundlich B, Singh A. Improvements in patient-reported outcomes, symptoms of depression and anxiety, and their association with clinical remission among patients with moderate-to-severe active early rheumatoid arthritis. *Rheumatology (Oxford)*. Feb; 2011 50(2):401–409. [PubMed: 21059675]
20. Matcham F, Norton S, Scott DL, Steer S, Hotopf M. Symptoms of depression and anxiety predict treatment response and long-term physical health outcomes in rheumatoid arthritis: secondary analysis of a randomized controlled trial. *Rheumatology (Oxford)*. Sep 8; 2015 54(9):1615–1623. [PubMed: 26111111]
21. Levesque MC. Biologic rheumatoid arthritis therapies: do we need more comparative effectiveness data? *BioDrugs*. Apr 1; 2012 26(2):65–70. [PubMed: 22385403]
22. Rathbun AM, Harrold LR, Reed GW. Temporal Effect of Depressive Symptoms on the Longitudinal Evolution of Rheumatoid Arthritis Disease Activity. *Arthritis care & research*. 2015; 67(6):765–775. [PubMed: 25384985]
23. Kremer J. The CORRONA database. *Ann Rheum Dis*. Nov; 2005 64(Suppl 4):iv37–41. [PubMed: 16239384]
24. Kobau R, Safran MA, Zack MM, Moriarty DG, Chapman D. Sad, blue, or depressed days, health behaviors and health-related quality of life, Behavioral Risk Factor Surveillance System, 1995-2000. *Health Qual Life Outcomes*. Jul 30; 2004 2:40. [PubMed: 15285812]
25. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care*. Nov; 2003 41(11):1284–1292. [PubMed: 14583691]
26. Jones D, Vichaya EG, Cleeland CS, Cohen L, Thekdi SM, Wang XS, et al. Screening for depressed mood in patients with cancer using the MD Anderson Symptom Inventory: investigation of a practical approach for the oncologist. *J Oncol Pract*. Mar; 2014 10(2):e95–102. [PubMed: 24281151]
27. Mukerji SS, Duffy SA, Fowler KE, Khan M, Ronis DL, Terrell JE. Comorbidities in head and neck cancer: agreement between self-report and chart review. *Otolaryngol Head Neck Surg*. Apr; 2007 136(4):536–542. [PubMed: 17418247]

28. Margolis KL, Lihong Q, Brzyski R, Bonds DE, Howard BV, Kempainen S, et al. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. *Clin Trials*. 2008; 5(3):240–247. [PubMed: 18559413]
29. Rathbun AM, Harrold LR, Reed GW. Temporal associations between the different domains of rheumatoid arthritis disease activity and the onset of patient-reported depressive symptoms. *Clin Rheumatol*. 2014:1–11.
30. Zimmerman M, Ruggero CJ, Chelminski I, Young D, Posternak MA, Friedman M, et al. Developing brief scales for use in clinical practice: the reliability and validity of single-item self-report measures of depression symptom severity, psychosocial impairment due to depression, and quality of life. *J Clin Psychiatry*. Oct; 2006 67(10):1536–1541. [PubMed: 17107244]
31. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther*. 2005; 7(4):R796–806. [PubMed: 15987481]
32. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, et al. Rheumatoid arthritis disease activity measures: american college of rheumatology recommendations for use in clinical practice. *Arthritis Care Res (Hoboken)*. May; 2012 64(5):640–647. [PubMed: 22473918]
33. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. *Arthritis Rheum*. Feb; 2006 54(2):600–606. [PubMed: 16447237]
34. Wolfe F, Michaud K. Predicting depression in rheumatoid arthritis: the signal importance of pain extent and fatigue, and comorbidity. *Arthritis Rheum*. May 15; 2009 61(5):667–673. [PubMed: 19404997]
35. Aletaha D, Funovits J, Ward M, Smolen J, Kvien T. Perception of improvement in patients with rheumatoid arthritis varies with disease activity levels at baseline. *Arthritis Care & Research*. 2009; 61(3):313–320. [PubMed: 19248136]
36. Anderson J, Sayles H, Curtis JR, Wolfe F, Michaud K. Converting modified health assessment questionnaire (HAQ), multidimensional HAQ, and HAQII scores into original HAQ scores using models developed with a large cohort of rheumatoid arthritis patients. *Arthritis Care Res (Hoboken)*. Oct; 2010 62(10):1481–1488. [PubMed: 20496428]
37. Hernan MA, Robins JM. Estimating causal effects from epidemiological data. *J Epidemiol Community Health*. Jul; 2006 60(7):578–586. [PubMed: 16790829]
38. Lee BK, Lessler J, Stuart EA. Weight trimming and propensity score weighting. *PLoS One*. Mar 31; 2011 6(3):e18174. [PubMed: 21483818]
39. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009; 28:3083–3107. [PubMed: 19757444]
40. Krishnan E, Fries JF. Measuring effectiveness of drugs in observational databanks: promises and perils. *ARTHRITIS RESEARCH AND THERAPY*. 2004; 6(2):41–85. [PubMed: 15059263]
41. Mitchell AJ, Coyne JC. Do ultra-short screening instruments accurately detect depression in primary care? A pooled analysis and meta-analysis of 22 studies. *Br J Gen Pract*. Feb; 2007 57(535):144–151. [PubMed: 17263931]
42. Julian LJ, Yelin E, Yazdany J, Panopalis P, Trupin L, Criswell LA, et al. Depression, medication adherence, and service utilization in systemic lupus erythematosus. *Arthritis Rheum*. Feb 15; 2009 61(2):240–246. [PubMed: 19177526]
43. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000; 11(5):550–560. [PubMed: 10955408]
44. Hill S, Dziedzic K, Thomas E, Baker SR, Croft P. The illness perceptions associated with health and behavioural outcomes in people with musculoskeletal hand problems: findings from the North Staffordshire Osteoarthritis Project (NorStOP). *Rheumatology (Oxford)*. Jun; 2007 46(6):944–951. [PubMed: 17308311]
45. Hale ED, Treharne GJ, Kitas GD. The common-sense model of self-regulation of health and illness: how can we use it to understand and respond to our patients' needs? *Rheumatology (Oxford)*. Jun; 2007 46(6):904–906.

Figure. 1.
Study Flowchart

Table 1

Baseline characteristics of patients initiating their first observed biologic DMARD in the CORRONA registry during follow-up with and without prevalent depressive symptoms.

Variable (n, %)	Controls (N=1,391)		Depressive Symptoms (N=291)		P
Female	1,036	74.48%	244	83.85%	0.001
<i>Race/Ethnicity</i>					0.69
White	1,187	85.33%	240	83.61%	
Hispanic	72	5.18%	20	6.87%	
Black	85	6.11%	20	6.87%	
Asian	22	1.58%	4	1.37%	
Other	25	1.80%	7	2.41%	
Age ^I (yrs)	57.61	12.73	54.85	11.45	0.0006
<i>Education</i>					0.037
Primary	72	5.18%	6	2.06%	
High School	553	39.76%	118	40.55%	
College/University	766	55.07%	162	57.39%	
<i>Insurance</i>					0.004
None	30	2.16%	5	1.72%	
Medicaid	27	1.94%	16	5.50%	
Medicare	234	16.82%	54	18.56%	
Private	1,100	79.08%	216	74.23%	
<i>Marital Status</i>					0.059
Single	155	11.14%	40	13.75%	
Married/Partnered	972	69.88%	180	61.86%	
Widowed	104	7.48%	30	10.31%	
Divorced/Separated	160	11.50%	41	14.09%	
<i>Employment</i>					<0.001
Full Time	599	43.06%	79	27.51%	
Part Time	132	9.49%	27	9.28%	
Unemployed	160	11.50%	38	13.06%	
Student	7	0.50%	3	1.01%	
Disabled	138	9.92%	92	31.62%	
Retired	355	25.52%	52	17.87%	
<i>CDAI</i>					<0.001
Low	324	23.29%	42	14.43%	
Moderate	551	39.61%	101	34.71%	
Severe	516	37.10%	148	50.86%	
Disease Duration ^I (years)	10.35	9.79	9.91	9.07	0.49

Variable (n, %)	Controls (N=1,391)		Depressive Symptoms (N=291)		P
Alcohol Use	846	44.64%	109	37.46%	0.023
Smoking	315	16.62%	76	26.12%	<0.001
<i>Exercise</i>					0.001
None	444	31.92%	128	43.99%	
1-2 times/week	417	29.98%	85	29.21%	
3-4 times/week	294	21.14%	44	15.12%	
5-6 times/week	89	6.40%	11	3.78%	
Daily	147	10.57%	23	7.90%	
BMI (kg/m ²)	28.79	6.81	31.26	8.65	<0.001
Comorbidity ²	1	[0-1]	1	[0-2]	<0.001
Antidepressant Use	108	7.76%	155	53.26%	<0.001

1682 depressed (n=291) and non-depressed control (n=1,391) patients in low, moderate, and severe disease activity at treatment initiation.

¹Continuous value given as the mean value and standard deviation

²Continuous value given as the median and IQR.

Table 2

Concomitant treatment characteristics by depressive symptom status at the time of treatment initiation.

Variable (n, %)	¶Controls (N=1,391)		Depressive Symptoms (N=291)		P Value
Biologic Naïve	756	54.35%	129	44.33%	0.02
Anti-TNF	1,075	77.28%	214	73.54%	0.17
Combination Therapy	1,132	81.38%	212	72.85%	0.001
Prednisone Use	474	34.08%	118	40.55%	0.035
Methotrexate Use	929	66.79%	170	58.42%	0.006
Biologic Agent					
Etanercept	271	19.48%	68	23.37%	0.31
Adalimumab	446	32.06%	85	29.21%	
Infliximab	256	18.40%	38	13.06%	
Certolizumab	55	3.95%	10	3.44%	
Golimumab	47	3.38%	13	4.47%	
Tocilizumab	29	2.08%	7	2.41%	
Abatacept	199	14.31%	46	15.81%	
Anakinra	6	0.43%	1	0.34%	
Rituximab	82	5.90%	23	7.90%	
# Prior Biologies	0.02				
0	761	54.71%	129	44.33%	
1	422	30.34%	95	32.65%	
2	144	10.35%	45	15.46%	
>3	64	4.60%	22	7.56%	

1682 depressed (n=291) and non-depressed control (n=1,391) patients in low, moderate, and severe disease activity at treatment initiation.

Table 3

Odds ratios for CDAI remission and low disease activity at 6 and 12 months after biologic DMARD initiation by self-reported depressive symptom status.

Depressive Symptoms	N	Remission Rate	Discontinuation Rate	Unadjusted OR	Weighted OR
<i>Remission at 6 Months</i>					
No	1,244	15.51%	30.55%	-	-
Yes	253	5.53%	32.41%	0.31 [0.18-0.55]	0.43 [0.19-0.96]
<i>Remission at 12 Months</i>					
No	1,101	16.71%	41.69%	-	-
Yes	220	10.00%	46.82%	0.55 [0.34-0.88]	0.83 [0.43-1.60]
<i>LDA at 6 Months</i>					
No	957	36.99%	29.47%	-	-
Yes	218	24.31%	32.57%	0.54 [0.39-0.76]	0.91 [0.56-1.47]
<i>LDA at 12 Months</i>					
No	837	35.84%	41.70%	-	-
Yes	183	21.86%	48.09%	0.50 [0.34-0.73]	0.87 [0.51-1.49]

Table 4

The unadjusted (β^1) and weighted (β^2) model based estimations of 6- and 12-months core component disease activity measure change from baseline by depressive symptom status at treatment initiation and corresponding standard differences (D) among the CDAI remission sample.

$\ddagger$ 6 Months						
Measure	β^1	P	D	β^2	P	D
SJC ^{A1}	2.9 [2.6-3.2]	0.75	0.01	2.9 [2.6-3.2]	0.35	0.04
SJC ^{B1}	2.8 [2.1-3.5]			3.5 [2.2-4.8]		
TJC ^{A1}	2.8 [2.4-3.1]	0.53	0.02	2.7 [2.4-3.1]	0.32	0.04
TJC ^{B1}	3.1 [2.2-3.9]			3.5 [2.0-5.1]		
PGA ^{A1}	9.8 [8.2-11.3]	0.45	0.02	10.5 [8.8-12.1]	0.18	0.05
PGA ^{B1}	8.3 [5.0-11.7]			6.8 [1.7-12.0]		
EGA ^{A1}	14.0 [12.8-15.2]	0.26	0.03	14.0 [12.7-15.3]	0.47	0.02
EGA ^{B1}	12.4 [9.8-15.0]			12.6 [8.9-16.2]		
$\ddagger$ 12 Months						
SJC ^{A2}	3.2 [2.8-3.5]	0.20	0.04	3.1 [2.8-3.5]	0.50	0.03
SJC ^{B2}	2.6 [1.8-3.4]			3.6 [2.2-5.1]		
TJC ^{A2}	3.0 [2.6-3.4]	0.51	0.02	3.0 [2.6-3.4]	0.63	0.02
TJC ^{B2}	2.6 [1.7-3.6]			3.4 [1.8-5.1]		
PGA ^{A2}	9.8 [8.1-11.4]	0.24	0.03	10.1 [8.3-12.0]	0.44	0.03
PGA ^{B2}	7.3 [3.7-11.0]			7.9 [2.5-13.2]		
EGA ^{A2}	14.1 [12.8-15.4]	0.01	0.07	13.9 [12.5-15.3]	0.09	0.06
EGA ^{B2}	10.0 [7.0-12.9]			10.5 [6.7-14.2]		

^{A1} No symptoms of depression 6 months (n=1,244)

^{B1} Prevalent depressive Symptoms 6 Months (n=253)

^{A2} No symptoms of depression 12 months (n=1,101)

^{B2} Prevalent depressive Symptoms 12 months (n=220)

$\ddagger$ Restricted to patients in low, moderate, and severe disease activity at baseline.

Table 5

The unadjusted (β^1) and weighted (β^2) model based estimations of 6- and 12-months core component disease activity measure change from baseline by depressive symptom status at treatment initiation and corresponding standard differences (D) among the CDAI LDA sample.

$\ddagger$ 6 Months						
Measure	β^1	P	D	β^2	P	D
SJC ^{A1}	3.8 [3.5-4.2]	0.34	0.03	3.7 [3.4-4.1]	0.35	0.04
SJC ^{B1}	3.4 [2.6-4.2]			4.4 [3.0-5.8]		
TJC ^{A1}	3.8 [3.3-4.2]	0.99	0.00	3.7 [3.2-4.2]	0.29	0.05
TJC ^{B1}	3.8 [2.8-4.7]			4.6 [3.0-6.2]		
PGA ^{A1}	13.0 [11.2-14.7]	0.36	0.03	13.4 [11.5-15.3]	0.28	0.04
PGA ^{B1}	11.1 [7.4-14.8]			10.2 [4.6-15.8]		
EGA ^{A1}	17.5 [16.1-18.9]	0.09	0.05	17.4 [15.8-18.9]	0.51	0.02
EGA ^{B1}	14.8 [11.9-17.8]			15.9 [12.2-19.8]		
$\ddagger$ 12 Months						
SJC ^{A2}	4.3 [3.8-4.7]	0.07	0.06	4.2 [3.7-4.6]	0.36	0.05
SJC ^{B2}	3.3 [2.4-4.2]			4.9 [3.3-6.5]		
TJC ^{A2}	4.1 [3.6-4.6]	0.27	0.03	4.1 [3.6-4.6]	0.61	0.03
TJC ^{B2}	3.4 [2.3-4.5]			4.6 [2.8-6.4]		
PGA ^{A2}	12.4 [10.4-14.4]	0.16	0.04	12.6 [10.4-14.7]	0.50	0.03
PGA ^{B2}	9.1 [4.9-13.2]			10.2 [3.7-16.7]		
EGA ^{A2}	17.7 [16.1-19.2]	0.004	0.09	17.3 [15.6-19.0]	0.09	0.06
EGA ^{B2}	12.3 [8.9-15.6]			13.6 [9.6-17.6]		

^{A1} No symptoms of depression 6 months (n=957)

^{B1} Prevalent depressive Symptoms 6 Months (n=218)

^{A2} No symptoms of depression 12 months (n=837)

^{B2} Prevalent depressive Symptoms 12 months (n=183)

$\ddagger$ Restricted to patients in moderate-to-severe disease activity at baseline.