




Posttraumatic Stress Disorder, Depression, Anxiety, and Persistence of Methotrexate and TNF Inhibitors in Patients with Rheumatoid Arthritis

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Objective. To examine the relationship of posttraumatic stress disorder (PTSD) with earlier treatment discontinuation and medication adherence in US veterans with rheumatoid arthritis (RA).

Methods. Veterans Affairs (VA) administrative data (2005–2014) were used to define unique dispensing episodes of methotrexate (MTX) and tumor necrosis factor inhibitors (TNFi) for veterans with RA. Diagnosis codes were used to categorize patients into mutually exclusive groups: PTSD (with/without depression/anxiety), depression/anxiety without PTSD, and neither psychiatric diagnosis. Multivariable Cox proportional hazards models were used to evaluate associations between psychiatric diagnoses and time to disease-modifying antirheumatic drug discontinuation (lapse in refill >90 days). Multivariable logistic regression was used to examine associations of diagnoses with medication nonadherence (proportion of days covered <0.8).

Results. There were 15081 dispensing episodes of MTX and 8412 dispensing episodes of TNFi. PTSD was independently associated with a greater likelihood of earlier discontinuation of both MTX (hazard ratio [HR] 1.15 [1.10–1.21]) and TNFi (HR 1.20 [1.13–1.28]). Depression/anxiety had a comparable risk of discontinuation for both MTX (HR 1.14 [1.10–1.19]) and TNFi (HR 1.16 [1.10–1.22]). Depression/anxiety, but not PTSD, was associated with higher odds of MTX (odds ratio [OR] 1.12 [1.03–1.22]) and TNFi (OR 1.14 [1.02–1.27]) nonadherence.

Conclusion. Veterans with RA and comorbid PTSD, depression, or anxiety had poor persistence of MTX and TNFi therapies. These results suggest that earlier discontinuation and low adherence to therapy among patients with RA with these psychiatric comorbidities may contribute to worse disease outcomes. Mechanisms by which these comorbidities contribute to lower adherence deserve further investigation and may lead to targeted interventions to improve disease outcomes.

INTRODUCTION

Individuals with rheumatoid arthritis (RA) appear to have a higher prevalence of psychiatric comorbidity (1). Furthermore, psychiatric comorbidity appears to be a predictive factor for poor outcomes and higher levels of disease activity in RA (2–4). These poor health outcomes include greater pain, more functional dis-

ability, and lower health-related quality of life (4). Posttraumatic stress disorder (PTSD) is a psychiatric disorder occurring as a result of traumatic experiences and has been associated with worse patient-reported outcomes and higher tender joint counts in RA (5). Recent work has also demonstrated that patients with RA who have comorbid PTSD express higher levels of proinflammatory cytokines, even compared with patients with other forms

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SIGNIFICANCE & INNOVATIONS

- Posttraumatic stress disorder (PTSD), a prevalent condition in the US veteran population, has been associated with worse disease outcomes among those with rheumatoid arthritis (RA).
- This is the first study to date to comprehensively examine the relationship between PTSD and disease-modifying antirheumatic drug (DMARD) persistence in US veterans with RA.
- In this retrospective cohort study using national VA data, comorbid PTSD, depression, and anxiety were associated with a higher risk of earlier DMARD discontinuation in RA.
- Depression and anxiety, but not PTSD, were significantly associated with a greater risk of poor adherence to methotrexate and tumor necrosis factor inhibitors.

of anxiety or depression (6). The prevalence of PTSD in US veterans is approximately 5% to 20% (7–9), which appears to be higher than the 1% to 12% lifetime prevalence in the general population (10), making this population of particular interest.

Although PTSD appears to be associated with more severe and symptomatic RA, the mechanisms underlying this relationship are not fully understood. In other chronic disorders, PTSD has been associated with reduced medication adherence (11), suggesting that suboptimal adherence or decreased drug persistence could serve as an explanation for these earlier observations. The relationship between related psychiatric conditions such as depression/anxiety and disease-modifying antirheumatic drug (DMARD) discontinuation has been studied with conflicting results (12–15).

Thus, the relationship of PTSD with DMARD persistence and medication adherence in RA warrants further investigation. To our knowledge, the literature to date has not examined the relationship between PTSD and persistence of DMARD therapy in patients with RA. The purpose of this study, therefore, was to examine the association between PTSD and DMARD persistence as compared with other psychiatric conditions while accounting for comorbidity and other potential confounders among US veterans with RA.

PATIENTS AND METHODS

Study design and setting. We conducted a retrospective cohort study using clinical data from January 2005 through January 2014 that were extracted from national Veterans Affairs (VA) administrative databases of US veterans with RA. Data were compiled from three national VA databases: the Corporate Data Warehouse (CDW), the Decision Support System National Pharmacy Extract, and the Pharmacy Benefits Management database. The Veterans Affairs Rheumatoid Arthritis Registry from which data were obtained has received institutional review board approval at all involved sites. All study subjects provided written informed

consent before enrollment. Patients with at least one diagnostic code for RA in the 12 months prior to the initiation of RA therapy were included in the analysis (*International Classification of Diseases*, 9th edition, 714.xx). This approach of classification has been previously demonstrated to yield a positive predictive value of 81% to 97% for identifying RA (16).

Medication exposures. Unique dispensing episodes of methotrexate (MTX), self-injectable tumor necrosis factor inhibitors (TNFi; adalimumab, etanercept, golimumab, certolizumab), hydroxychloroquine (HCQ), sulfasalazine (SSZ), leflunomide, and prednisone were extracted from pharmacy dispensing records. Analyses focused on the first dispensing episode for MTX or individual TNFi therapies. This focus was predicated on the role of MTX as a cornerstone therapy in RA (17). Likewise, TNFi agents are generally accepted to represent first-line biologic therapies (17). Some patients switched TNFi agents over time and thus may have accounted for multiple courses of TNFi. Self-injectable TNFi were chosen for analysis rather than intravenous TNFi because of the ability to more precisely define treatment course length given pharmacy dispensing records of self-injectables. Other DMARDs included in the analysis as covariables were selected based on their established role as conventional DMARDs in the management of RA (17).

Identification of PTSD and other psychiatric diagnoses. Psychiatric diagnosis codes and other diagnosis codes were extracted from CDW (using all available CDW data), and diagnoses were defined based on previously published algorithms any time prior to the drug course start date or up to 1 year after (5). Patients with RA were categorized into one of three mutually exclusive groups: PTSD (with or without depression/anxiety), depression and/or anxiety without PTSD, or neither psychiatric diagnosis. The PTSD group was defined as having an ICD-9 code of 309.81. The positive predictive value of this definition of PTSD has previously been reported to be between approximately 75% and 82%, the latter value based on the use of two codes separated in time (18). The depression and/or anxiety without PTSD group included major depressive disorder (codes 296.2 to 296.36), other unspecified episodic mood disorder (code 296.90), anxiety states (code 300.0x), adjustment reaction (code 309.xx), and depressive disorder not otherwise classified (code 311.xx), excluding code 309.81. Patients without any of the aforementioned diagnoses were classified as having neither psychiatric diagnosis and thus served as a control group. This study focused specifically on the effects of PTSD, depression, and anxiety on DMARD adherence, and no exclusions were made based on the presence of codes for other psychiatric conditions.

Definition of drug persistence and adherence. The number of medication doses dispensed and the expected treatment duration were calculated for each DMARD dispensing episode. For each dispensing episode, the expected duration of

drug supply was based on the number of doses dispensed and associated dosing instructions. Each drug treatment course was defined by the duration of time in which there was not a 90-day lapse between the end of one dispensing episode and the start of the next dispensing episode (19). Therefore, drug discontinuation was defined as a lapse in drug refill greater than 90 days. Drug persistence (or drug survival) served as the primary outcome of interest and was defined as the time between the dates of the first DMARD dispensing episode and the expected end of the last drug supply for an individual DMARD. Patient follow-up was censored at the time of death, at the end of health care follow-up coinciding with the last available diagnosis code data, or at study end date (January 2014). An individual patient could contribute only one treatment course for each of the individual DMARDs examined.

Given the potential relationship between adherence and drug survival, the proportion of days covered (PDC) was examined as a measure of treatment adherence. PDC is the ratio of number of days “covered by a medication” to the number of days in an observation period (20). Low adherence was defined as a PDC less than 80%, a generally accepted delineator between adequate and suboptimal adherence (21,22). PDC was calculated over the entirety of each drug treatment course with additional sensitivity analyses for drug courses of at least 6- and 12-month durations.

Potential confounders. Covariates of interest were derived from VA administrative and clinical laboratory databases. Previously hypothesized confounders that may impact disease activity in RA were included (23). Covariates included RA disease duration (>5 versus <5 years; defined as time elapsed between an initial diagnosis code for RA and treatment initiation), comorbidity, body mass index (BMI, kg/m²), smoking status (current versus other), calendar year (2010-2014 versus 2005-2009), age, sex, race (White vs. Black/other), anticyclic citrullinated peptide antibody (anti-CCP) serostatus, C-reactive protein (CRP) concentration, and concurrent DMARD use. Calendar year of treatment initiation was included to account for temporal trends in diagnosis of psychiatric conditions and in DMARD use, which might affect treatment discontinuation. Comorbid conditions examined as covariates included congestive heart failure, history of malignancy, diabetes, and hypertension and were defined by the presence of diagnosis codes as previously described (24,25). The Rheumatic Disease Comorbidity Index (RDCI) was examined as a measure of overall comorbidity burden (26). BMI was included as a covariate given recent work highlighting the relationship between BMI and DMARD persistence (23). Among those initiating TNFi, the specific biologic agent was examined as a covariate in addition to whether the treatment represented an initial versus subsequent biologic therapy.

Statistical analysis. Differences in patient characteristics according to psychiatric category were examined using chi-squared tests for categorical data and analysis of variance or Kruskal-Wallis tests as appropriate. Missing data for some

covariables (CRP, anti-CCP status, and disease duration) were imputed using multiple imputation with five iterations in order to avoid dropping otherwise informative observations.

Multivariable Cox proportional hazards models were used to evaluate associations between psychiatric diagnoses and time to DMARD discontinuation.

Partially adjusted models included calendar year, age, sex, race, and BMI as covariates in addition to the specific agent used and prior biologic use for analyses among TNFi users. In addition to the aforementioned variables, covariates in fully adjusted models included individual comorbidities, RDCI score, CRP, disease duration, anti-CCP antibody status, smoking status, and concurrent DMARD use. Based on prior results suggesting that the associations between PTSD and proinflammatory cytokine concentrations differ between seropositive and seronegative patients (6), additional fully adjusted persistence analyses were completed after stratifying patients based on anti-CCP antibody status. Patients with unknown anti-CCP antibody status were excluded from these stratified analyses. Plots of the cumulative incidence of discontinuation were generated using competing risks regression and stratified by the underlying psychiatric diagnosis.

Similarly, partially and fully adjusted logistic regression models were used to examine associations of psychiatric diagnoses with MTX and TNFi treatment adherence. Recognizing that early discontinuation can impact measures of adherence such as the PDC, sensitivity analyses were performed by limiting the analysis to patients with course lengths of at least 6 or 12 months in duration. Limiting analyses to drug courses that persisted for more than 6 or 12 months helps to limit the effect of factors that may drive poor adherence in the early months of DMARD therapy (initial cost burden, new medication side effects, adjustment to previous medication routines, etc).

Analyses were performed within the VA Informatics and Computing Infrastructure using Stata 15.1 software (StataCorp, LP).

RESULTS

There were 15081 dispensing episodes of MTX in 15081 unique patients and 8412 dispensing episodes of TNFi in 7092 unique patients. There were 12842 discontinuations among MTX users over 31976 person-years of follow-up with a median time to discontinuation of 1.30 years. There were 7286 discontinuations of TNFi over 17174 years of follow-up with a median time to discontinuation of 1.18 years. Patient characteristics based on treatment and psychiatric diagnoses are shown in Tables 1 and 2. Comorbid PTSD was observed in 16% (2472 of 15081) of those initiating MTX and 18% (1514 of 8412) of those initiating TNFi. Depression and/or anxiety (without PTSD) was seen in 30% (4453 of 15081) of those initiating MTX and 33% (2780 of 8412) of those initiating TNFi. Drug courses in the TNFi group were more common in the later years between 2010 and 2014 than the MTX group (46%

Table 1. Patient characteristics among patients with rheumatoid arthritis initiating methotrexate (n = 15081)

	Neither Psychiatric Diagnosis (n = 8156)	Depression/Anxiety Without PTSD (n = 4453)	PTSD (n = 2472)	P value
Demographics				
Age, y	64.7 (11.4)	60.9 (11.8)	59.5 (10.2)	<0.001
Male, n (%)	7480 (92%)	3666 (82%)	2127 (86%)	<0.001
White race, n (%)	6153 (75%)	3336 (75%)	1739 (70%)	<0.001
Health characteristics and comorbidity				
BMI, kg/m ²	28.8 (5.5)	29.7 (6.1)	30.3 (5.9)	<0.001
CHF, n (%)	629 (8%)	439 (10%)	183 (7%)	<0.001
Diabetes, n (%)	2056 (25%)	1288 (29%)	822 (33%)	<0.001
Hypertension, n (%)	5438 (67%)	3064 (69%)	1760 (71%)	<0.001
RDCI, median (IQR)	1 (0, 2)	2 (1, 3)	2 (1, 3)	<0.001
Calendar year 2010-2014 (vs. 2005-2009), n (%) ^a	2670 (33%)	1788 (40%)	1114 (45%)	<0.001
Disease duration >5 years, (%) ^b	25%	26%	23%	0.068
Current smoker, n (%)	944 (12%)	785 (18%)	537 (22%)	<0.001
History of malignancy, n (%)	1050 (13%)	657 (15%)	341 (14%)	0.012
Anti-CCP positive, (%) ^b	64%	57%	57%	0.092
CRP ^b	2.4 (3.4)	2.2 (3.3)	2.2 (3.3)	0.063
Concurrent medications, n (%)				
Prednisone	2984 (37%)	1743 (39%)	922 (37%)	0.018
Methotrexate	N/A	N/A	N/A	N/A
TNFi	735 (9%)	436 (10%)	194 (8%)	0.026
Hydroxychloroquine	1099 (13%)	719 (16%)	443 (18%)	<0.001
Sulfasalazine	330 (4%)	222 (5%)	136 (6%)	0.003
Leflunomide	154 (2%)	82 (2%)	39 (2%)	0.597

Note. Values are reported as percentages and mean (SD) unless otherwise noted.

Abbreviations: anti-CCP = anti-cyclic citrullinated peptide antibody; BMI = body mass index; CHF = congestive heart failure; CRP = C-reactive protein; IQR = interquartile range; PTSD = posttraumatic stress disorder; RDCI = Rheumatic Disease Comorbidity Index; TNFi = self-injectable tumor necrosis factor inhibitor.

^a Calendar date of the start of course observation.

^b Includes imputed values.

versus 37%). The TNFi group was more likely to have a disease duration of more than 5 years (38% versus 25%) and to be anti-CCP positive (68% versus 61%) as compared with the MTX group.

Patients with PTSD or depression/anxiety were generally younger, more likely to be female, had higher BMI, had more comorbidity, were more likely to smoke, and were more likely to start drug courses in later years. Those with comorbid psychiatric diagnoses were also generally less likely to be anti-CCP antibody positive. Among those initiating TNFi, patients with comorbid psychiatric diagnoses were also generally less likely to be initiating their first TNFi course (Tables 1 and 2).

Associations of psychiatric diagnosis with treatment discontinuation are shown in Table 3. In partially adjusted models, PTSD was associated with a greater likelihood of discontinuing both MTX (hazard ratio [HR]: 1.19; [95% confidence interval [CI]: 1.13, 1.25]; $P < 0.001$) and TNFi (HR: 1.25; [1.17, 1.33]; $P < 0.001$). Depression/anxiety without PTSD yielded similar associations with discontinuation of MTX (HR 1.18 [1.13, 1.23]; $P < 0.001$) and TNFi (HR 1.19 [1.13, 1.26]; $P < 0.001$). These associations persisted in fully adjusted models. Specifically, following full adjustment, PTSD was associated with a greater likelihood of discontinuing both MTX (HR 1.15 [1.10, 1.21]; $P < 0.001$) and TNFi (HR 1.20 [1.13, 1.28];

$P < 0.001$). The risk of discontinuation with depression/anxiety (without PTSD) was comparable with that observed for PTSD for both MTX (HR 1.14 [1.10, 1.19]; $P < 0.001$) and TNFi (HR 1.16 [1.10, 1.22]; $P < 0.001$) in fully adjusted models (Table 3). Overall, results were similar in fully adjusted models stratified by anti-CCP status, although the associations of psychiatric comorbidities with treatment persistence were slightly attenuated and did not achieve significance in anti-CCP antibody-negative patients (Figure 1).

Other factors that were observed to be associated with a greater likelihood of early discontinuation of MTX included younger age (versus 60-80 years), female sex, Black/other race, underweight BMI, later calendar year, congestive heart failure, current smoking, greater comorbidity (RDCI), anti-CCP negative serostatus, and concurrent TNFi use (Table 3). Among drug courses of TNFi, other factors associated with a greater likelihood of early discontinuation included younger age (versus 60-70 years), female sex, Black/other race, normal BMI (20-25 kg/m²), prior biologic use, greater comorbidity (RDCI), history of malignancy, current smoking, certolizumab use (versus adalimumab), concurrent use of prednisone, concurrent use of leflunomide, and the absence of concurrent MTX (Table 3).

Associations of comorbid psychiatric conditions with DMARD adherence are summarized in Table 4. Depression/anxiety in the

Table 2. Patient characteristics among patients with rheumatoid arthritis initiating TNFi (n = 8412)

	Neither Psychiatric Diagnosis (n = 4118)	Depression/Anxiety Without PTSD (n = 2780)	PTSD (n = 1514)	P value
Demographics				
Age, y	62.0 (10.6)	58.7 (11.1)	58.4 (9.1)	<0.001
Male, n (%)	3730 (91%)	2276 (82%)	1289 (85%)	<0.001
White race, n (%)	3241 (79%)	2152 (77%)	1069 (71%)	<0.001
Health characteristics and comorbidity				
BMI, kg/m ²	29.5 (5.7)	30.2 (6.2)	31.0 (6.2)	<0.001
CHF, n (%)	268 (7%)	215 (8%)	86 (6%)	0.025
Diabetes, n (%)	1053 (26%)	829 (30%)	523 (35%)	<0.001
Hypertension, n (%)	2772 (67%)	1888 (68%)	1104 (73%)	<0.001
RDCl, median (IQR)	1 (0, 2)	2 (1, 3)	2 (1, 3)	<0.001
Calendar year 2010-2014 (vs. 2005-2009), n (%) ^a	1731 (42%)	1311 (47%)	791 (52%)	<0.001
Disease duration >5 years, (%) ^b	38%	39%	36%	0.788
Current smoker, n (%)	680 (17%)	620 (22%)	359 (24%)	<0.001
History of malignancy, n (%)	423 (10%)	308 (11%)	168 (11%)	0.483
Anti-CCP positive, (%) ^b	72%	65%	63%	0.061
CRP ^b	1.9 (3.4)	2.0 (3.4)	1.9 (3.4)	0.856
First biologic, n (%)	2741 (67%)	1655 (60%)	932 (62%)	<0.001
Concurrent medications, n (%)				
Prednisone	1397 (34%)	970 (35%)	505 (33%)	0.549
Methotrexate	2227 (54%)	1378 (50%)	764 (50%)	0.001
TNFi	N/A	N/A	N/A	N/A
Hydroxychloroquine	686 (17%)	494 (18%)	287 (19%)	0.112
Sulfasalazine	338 (8%)	232 (8%)	122 (8%)	0.946
Leflunomide	334 (8%)	228 (8%)	129 (9%)	0.884

Note. Values are reported as percentages and mean (SD) unless otherwise noted.

Abbreviations: anti-CCP = anti-cyclic citrullinated peptide antibody; BMI = body mass index; CHF = congestive heart failure; CRP = C-reactive protein; IQR = interquartile range; PTSD = posttraumatic stress disorder; RDCl = Rheumatic Disease Comorbidity Index; TNFi = self-injectable tumor necrosis factor inhibitor.

^a Calendar date of the start of course observation.

^b Includes imputed values.

absence of PTSD was associated with a higher likelihood of low adherence (PDC < 80%) to MTX in fully adjusted models (OR 1.12 [1.03, 1.22]; $P = 0.006$). Similar associations were observed between depression/anxiety with low adherence to TNFi in fully adjusted models (OR 1.14 [1.02, 1.27]; $P = 0.02$). In contrast, in fully adjusted models PTSD was not significantly associated with low adherence to either MTX (OR 1.08 [0.97, 1.19]; $P = 0.16$) or TNFi (OR 1.08 [0.95, 1.23]; $P = 0.26$) (Table 4).

Other factors associated with greater odds of low adherence to MTX included younger age (versus > 60 years), Black/other race, overweight BMI versus severely obese BMI (25-30 versus ≥ 35 kg/m²), earlier calendar year, lack of hypertension, nonconcurrent smoking, concurrent TNFi use, and absence of concurrent sulfasalazine (Table 4). Among drug courses of TNFi, other factors associated with greater odds of low adherence included younger age (versus >60 years), Black/other race, earlier calendar year, lack of hypertension, use of etanercept (versus adalimumab), and absence of concurrent sulfasalazine (Table 4).

Recognizing that early discontinuation may impact longer-term measures of adherence, sensitivity analyses were undertaken requiring specified drug course durations of at least 6 and 12 months (Table 5). In patients who remained on therapy for these

specified durations, comorbid depression/anxiety and PTSD were both associated with lower treatment adherence for MTX and TNFi in fully adjusted models. For example, with drug courses longer than 1 year, depression/anxiety (without PTSD) was more strongly associated with low adherence to MTX (OR 1.29 [1.16, 1.43]; $P < 0.001$) and TNFi (OR 1.23 [1.07, 1.42]; $P = 0.004$). PTSD demonstrated a similar pattern of being associated with low adherence with drug courses longer than 1 year with MTX (OR 1.19 [1.05, 1.36]; $P = 0.009$) and TNFi (OR 1.33 [1.12, 1.59]; $P = 0.002$).

DISCUSSION

This large, national study of US veterans with RA demonstrated that PTSD, depression, and anxiety are associated with lower persistence with MTX and TNFi, even after accounting for confounding factors such as demographics and comorbidity. This heightened risk of earlier treatment discontinuation was similar in those with PTSD compared with those with depression and/or anxiety alone. The reduced persistence of therapy was also similar for courses of both MTX and TNFi. Although the magnitude of this risk may appear to be relatively small (14%-20%), it was similar in magnitude or stronger than the risk of discontinuation observed

Table 3. Multivariable Cox proportional hazards models evaluating the associations between psychiatric diagnosis and the time to MTX and TNFi discontinuation

	MTX Discontinuation HR (95% CI)		TNFi Discontinuation HR (95% CI)	
	Partially Adjusted ^a	Fully Adjusted ^b	Partially Adjusted ^a	Fully Adjusted ^b
Psychiatric diagnosis (vs. none)				
Depression/anxiety	1.18 (1.13, 1.23) ^c	1.14 (1.10, 1.19) ^c	1.19 (1.13, 1.26) ^c	1.16 (1.10, 1.22) ^c
PTSD	1.19 (1.13, 1.25) ^c	1.15 (1.10, 1.21) ^c	1.25 (1.17, 1.33) ^c	1.20 (1.13, 1.28) ^c
Age categories (vs. <60 y)				
60-70 y	0.84 (0.80, 0.87) ^c	0.82 (0.79, 0.86) ^c	0.91 (0.86, 0.96) ^c	0.89 (0.84, 0.94) ^c
70-80 y	0.92 (0.87, 0.96) ^d	0.88 (0.84, 0.93) ^c	0.96 (0.89, 1.04)	0.93 (0.85, 1.00)
>80 y	0.99 (0.92, 1.07)	0.94 (0.87, 1.02)	1.20 (1.04, 1.38) ^e	1.15 (0.99, 1.33)
Male sex	0.89 (0.84, 0.94) ^c	0.89 (0.84, 0.94) ^c	0.81 (0.76, 0.87) ^c	0.80 (0.74, 0.86) ^c
Black/other race (vs. White)	1.13 (1.07, 1.18) ^c	1.13 (1.07, 1.19) ^c	1.09 (1.01, 1.17) ^e	1.08 (1.00, 1.16) ^e
BMI categories (vs. 25-30 kg/m ²)				
<20 kg/m ²	1.12 (1.01, 1.26) ^e	1.13 (1.01, 1.26) ^e	1.15 (0.98, 1.35)	1.17 (1.00, 1.37)
20-25 kg/m ²	1.03 (0.98, 1.08)	1.04 (0.99, 1.09)	1.14 (1.06, 1.22) ^c	1.14 (1.06, 1.22) ^c
30-35 kg/m ²	1.00 (0.96, 1.05)	0.99 (0.94, 1.03)	1.03 (0.97, 1.09)	1.02 (0.96, 1.09)
≥35 kg/m ²	1.04 (0.99, 1.10)	1.01 (0.96, 1.07)	1.05 (0.98, 1.13)	1.03 (0.97, 1.11)
Calendar year (vs. 2005-2009)				
2010-2014	1.12 (1.08, 1.16) ^c	1.10 (1.05, 1.15) ^c	1.10 (1.04, 1.15) ^c	1.05 (0.99, 1.12)
Initial biologic use	0.85 (0.81, 0.89) ^c	0.86 (0.82, 0.91) ^c
Agent used (vs. adalimumab)				
Etanercept	0.97 (0.93, 1.02)	0.97 (0.92, 1.01)
Certolizumab	1.62 (1.36, 1.92) ^c	1.60 (1.35, 1.90) ^c
Golimumab	1.04 (0.88, 1.23)	1.02 (0.86, 1.20)
CHF	...	1.10 (1.02, 1.17) ^d	...	1.06 (0.96, 1.17)
Diabetes	...	1.00 (0.96, 1.04)	...	1.02 (0.97, 1.08)
Hypertension	...	0.99 (0.94, 1.03)	...	1.01 (0.95, 1.06)
History of malignancy	...	1.05 (1.00, 1.11)	...	1.11 (1.03, 1.20) ^d
RDCI	...	1.03 (1.01, 1.04) ^d	...	1.03 (1.01, 1.06) ^d
Disease duration >5 years	...	1.02 (0.97, 1.07)	...	0.98 (0.93, 1.03)
Current smoker	...	1.07 (1.01, 1.14) ^e	...	1.11 (1.04, 1.20) ^d
Anti-CCP positive	...	0.87 (0.82, 0.91) ^c	...	0.94 (0.86, 1.02)
CRP	...	1.00 (0.99, 1.00)	...	1.00 (0.99, 1.01)
Concurrent medications				
Prednisone	...	0.97 (0.93, 1.00)	...	1.12 (1.06, 1.17) ^c
Methotrexate	0.90 (0.86, 0.94) ^c
TNFi	...	1.07 (1.00, 1.13) ^e
Hydroxychloroquine	...	0.95 (0.91, 1.00)	...	0.98 (0.92, 1.05)
Sulfasalazine	...	1.05 (0.96, 1.14)	...	0.97 (0.89, 1.05)
Leflunomide	...	0.96 (0.85, 1.10)	...	1.13 (1.04, 1.23) ^d

Abbreviations: anti-CCP = anti-cyclic citrullinated peptide antibody; BMI = body mass index; CHF = congestive heart failure; CI = confidence interval; CRP = C-reactive protein; HCQ = hydroxychloroquine; HR = hazard ratio; LEF = leflunomide; MTX = methotrexate; PTSD = posttraumatic stress disorder; RDCI = Rheumatic Disease Comorbidity Index; SSZ = sulfasalazine; TNFi = self-injectable tumor necrosis factor inhibitor.

^a Adjusted for calendar date, age, sex, race, and BMI. For TNFi, also adjusted for drug name and initial versus subsequent biologic course.

^b Also adjusted for RDCI, CRP, disease duration >5 years, ever anti-CCP positive, concurrent medication use (MTX, prednisone, TNFi, HCQ, SSZ, LEF), diabetes, hypertension, CHF, history of malignancy, current smoking.

^c $P < 0.001$.

^d $P < 0.01$.

^e $P < 0.05$.

for female sex, Black race, BMI, anti-CCP antibody positivity, and other DMARD use.

The observation of lower persistence of drug therapy in patients with RA and comorbid PTSD is novel and builds upon prior studies of PTSD and depression being associated with poor medication adherence in other chronic conditions (27–30). While medication nonadherence may lead to lower medication persistence, the two are not synonymous because medications may be discontinued for several other reasons (ie, lack of efficacy, side effects, cost, etc). Our findings of lower persistence

and medication adherence in veterans with RA and depression are consistent with other, but not all, studies in RA (12–15). Patient-reported depression/anxiety was identified as a risk factor for biologic DMARD discontinuation in a large North American registry of patients with RA (13). A separate study also suggested that the poor persistence to TNFi observed in association with depression was largely attributable to a lack of efficacy (14). In contrast, another small study among persons with RA found no association between depression and DMARD discontinuation and actually suggested that patients with lower levels of reported

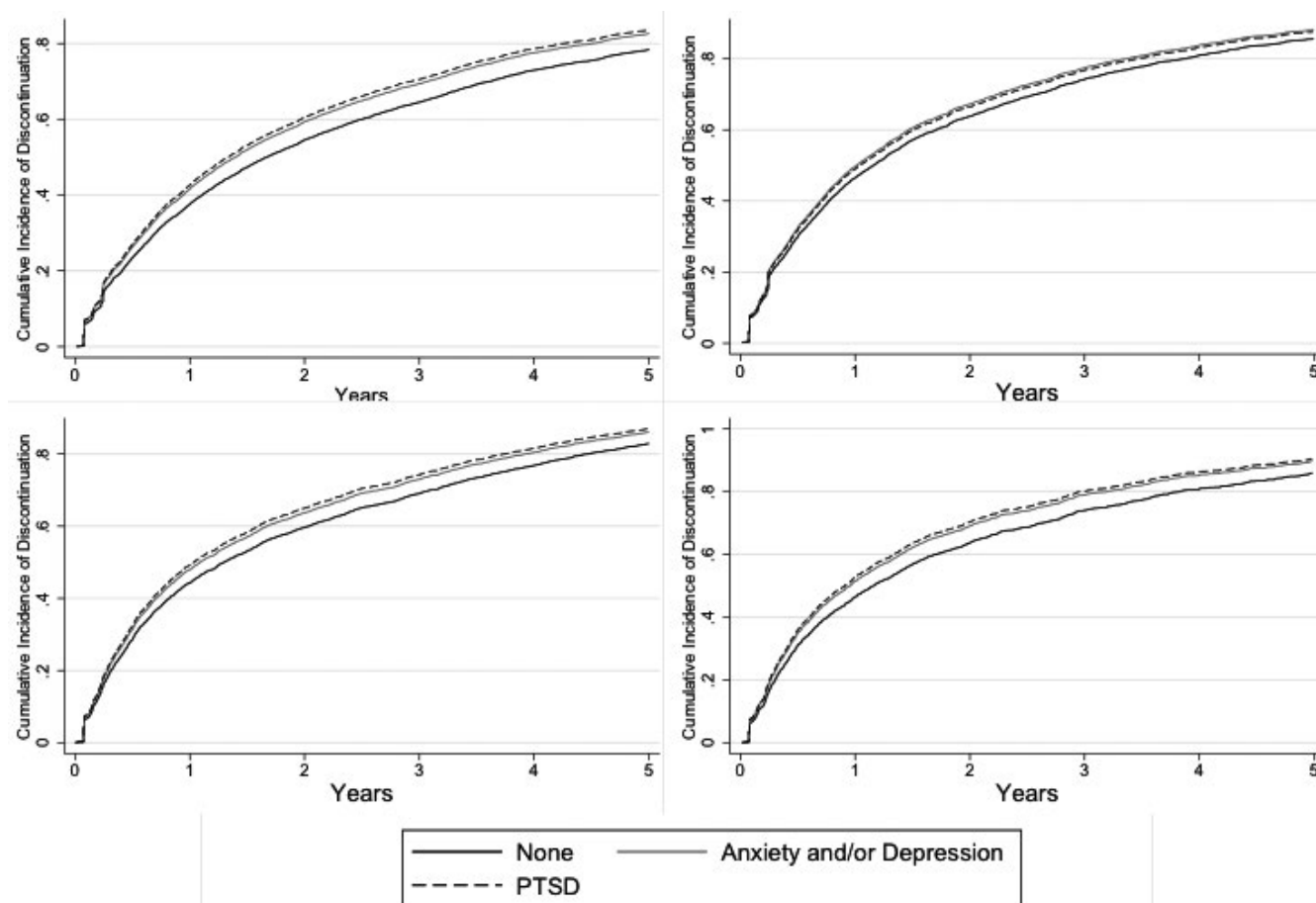


Figure 1. Cumulative incidence of MTX and TNFi discontinuation in anti-CCP antibody positive and negative patients. MTX discontinuation shown in top panels for anti-CCP antibody positive (top left) and anti-CCP antibody negative (top right). Among anti-CCP positive patients ($n=6,349$), corresponding adjusted HRs (vs. no psychiatric comorbidity) for MTX discontinuation are 1.18 (95% CI 1.06 to 1.27) for PTSD and 1.14 (95% CI 1.03 to 1.20) for depression/anxiety. TNFi discontinuation shown in bottom panels for anti-CCP antibody positive (bottom left) and anti-CCP antibody negative (bottom right). Among anti-CCP positive patients ($N=4,166$, corresponding adjusted HRs (vs. neither psychiatric comorbidity) for TNFi discontinuation are 1.16 (95% CI 1.09 to 1.27) for PTSD and 1.12 (95% CI 1.07 to 1.22) for depression/anxiety. MTX= Methotrexate; TNFi= self-injectable tumor necrosis factor inhibitor; Anti-CCP=Anti-cyclic citrullinated peptide antibody; HR=hazard ratio; 95%CI=95% Confidence Interval; PTSD= post-traumatic stress disorder.

anxiety were more likely to discontinue DMARDs at 1 year of follow-up (15).

While PTSD does not appear to infer a higher risk of DMARD discontinuation compared with depression and/or anxiety alone, there were differences in the effects of PTSD and depression/anxiety on drug adherence. While depression and anxiety were associated with low adherence to MTX and TNFi during the study period, PTSD was not significantly associated with low adherence in either partially or fully adjusted models. This suggests that, while discontinuation among those with depression and/or anxiety alone may be at least partially explained by a propensity for suboptimal adherence, the poor treatment persistence observed among those with comorbid PTSD does not appear to be as easily explained by low therapeutic adherence. Sensitivity analyses considering drug courses longer than 6 to 12 months demonstrated correlation between PTSD and low adherence similar to the effects accompanying depression/anxiety. It is conceivable

that other pathways explain poor drug persistence in PTSD, such as a more inflammatory phenotype of RA. Previous work that has demonstrated higher levels of inflammatory cytokines in patients with RA and PTSD might support this theory (6). Likewise, PTSD and depression have also been shown to be independent risk factors for developing incident RA (31–34), with at least one study suggesting this risk is tied to more prominent levels of psychosocial stress (34).

A potential contributor to the higher likelihood for MTX or TNFi discontinuation among those with PTSD, depression, and anxiety may be higher disease activity scores in this population that could lead to apparent inefficacy. Depression, for example, may contribute to higher pain and measured disease activity and therefore appear to decrease the efficacy of several available treatments (12). The contribution of PTSD to worse patient-reported outcomes and higher tender joint counts may play a similar role (5). Higher perceived disease activity would likely lead

Table 4. Multivariable logistic regression models evaluating associations between psychiatric diagnoses with low adherence to MTX and TNFi^a

	MTX Low Adherence OR (95% CI)		TNFi Low Adherence OR (95% CI)	
	Partially Adjusted ^b	Fully Adjusted ^c	Partially Adjusted ^b	Fully Adjusted ^c
Psychiatric diagnosis (vs. none)				
Depression/anxiety	1.11 (1.03, 1.21) ^d	1.12 (1.03, 1.22) ^d	1.14 (1.03, 1.27) ^e	1.14 (1.02, 1.27) ^e
PTSD	1.06 (0.96, 1.17)	1.08 (0.97, 1.19)	1.09 (0.95, 1.24)	1.08 (0.95, 1.23)
Age Categories (vs. <60 y)				
60-70 y	0.88 (0.81, 0.96) ^d	0.89 (0.82, 0.98) ^e	0.64 (0.58, 0.71) ^f	0.64 (0.57, 0.71) ^f
70-80 y	0.85 (0.76, 0.94) ^d	0.87 (0.78, 0.97) ^e	0.53 (0.45, 0.62) ^f	0.52 (0.44, 0.61) ^f
>80 y	0.79 (0.68, 0.91) ^d	0.81 (0.70, 0.95) ^d	0.46 (0.34, 0.63) ^f	0.46 (0.33, 0.63) ^f
Male sex	0.98 (0.87, 1.09)	0.99 (0.89, 1.11)	0.99 (0.86, 1.14)	1.00 (0.87, 1.15)
Black/other race (vs. White)	1.57 (1.43, 1.73) ^f	1.61 (1.46, 1.77) ^f	1.30 (1.13, 1.50) ^f	1.31 (1.14, 1.51) ^f
BMI categories (vs. 25-30 kg/m ²)				
<20 kg/m ²	1.05 (0.85, 1.30)	1.05 (0.84, 1.30)	0.99 (0.72, 1.37)	0.98 (0.70, 1.36)
20-25 kg/m ²	1.02 (0.93, 1.12)	1.01 (0.92, 1.12)	1.08 (0.94, 1.23)	1.07 (0.94, 1.23)
30-35 kg/m ²	0.93 (0.85, 1.02)	0.93 (0.85, 1.02)	0.91 (0.81, 1.03)	0.92 (0.82, 1.04)
≥35 kg/m ²	0.86 (0.77, 0.96) ^d	0.87 (0.78, 0.97) ^e	0.95 (0.83, 1.09)	0.96 (0.83, 1.10)
Calendar year (vs. 2005-2009)				
2010-2014	0.85 (0.79, 0.91) ^f	0.91 (0.83, 0.99) ^e	0.78 (0.71, 0.86) ^f	0.79 (0.71, 0.89) ^f
Initial biologic use	0.98 (0.89, 1.08)	1.02 (0.92, 1.13)
Agent used (vs. adalimumab)				
Etanercept	1.17 (1.07, 1.29) ^d	1.17 (1.06, 1.29) ^d
Certolizumab	1.20 (0.84, 1.71)	1.18 (0.82, 1.68)
Golimumab	1.10 (0.78, 1.54)	1.05 (0.75, 1.48)
CHF	...	1.06 (0.92, 1.21)	...	1.07 (0.88, 1.31)
Diabetes	...	0.98 (0.90, 1.07)	...	1.08 (0.96, 1.21)
Hypertension	...	0.90 (0.82, 0.97) ^e	...	0.89 (0.79, 0.99) ^e
History of malignancy	...	0.91 (0.82, 1.01)	...	0.98 (0.84, 1.15)
RDCI	...	1.02 (0.99, 1.05)	...	1.01 (0.97, 1.06)
Disease duration >5 years	...	1.02 (0.92, 1.13)	...	1.10 (0.99, 1.22)
Current smoker	...	0.87 (0.78, 0.99) ^e	...	1.02 (0.89, 1.18)
Anti-CCP positive	...	1.04 (0.95, 1.13)	...	0.99 (0.90, 1.10)
CRP	...	0.99 (0.98, 1.01)	...	1.00 (0.97, 1.03)
Concurrent medications				
Prednisone	...	0.98 (0.91, 1.05)	...	0.92 (0.83, 1.01)
Methotrexate	0.97 (0.88, 1.07)
TNFi	...	1.15 (1.01, 1.29) ^e
Hydroxychloroquine	...	0.91 (0.82, 1.01)	...	0.88 (0.77, 1.00)
Sulfasalazine	...	0.77 (0.65, 0.92) ^d	...	0.78 (0.66, 0.94) ^d
Leflunomide	...	0.91 (0.70, 1.18)	...	0.88 (0.74, 1.05)

Abbreviations: anti-CCP = anti-cyclic citrullinated peptide antibody; BMI = body mass index; CHF = congestive heart failure; CI = confidence interval; CRP = C-reactive protein; HCQ = hydroxychloroquine; LEF = leflunomide; MTX = methotrexate; OR = odds ratio; PTSD = posttraumatic stress disorder; RDCI = Rheumatic Disease Comorbidity Index; SSZ = sulfasalazine; TNFi = self-injectable tumor necrosis factor inhibitor.

^a Low adherence as defined by proportion of days covered (PDC) <80% over drug course.

^b Adjusted for calendar date, age, sex, race, and BMI. For TNFi, also adjusted for drug name and initial vs. subsequent biologic course.

^c Also adjusted for RDCI, CRP, disease duration >5 years, ever anti-CCP positive, concurrent medication use (MTX, prednisone, TNFi, HCQ, SSZ, LEF), diabetes, hypertension, CHF, history of malignancy, current smoking.

^d $P < 0.01$.

^e $P < 0.05$.

^f $P < 0.001$.

to drug course discontinuation and more frequent therapy adjustments over time. Depression and anxiety have been associated with less remission in RA as measured by Disease Activity Score (DAS)-44, a measure of disease activity, at 1 year (3). Moreover, persistent depression has been associated with less response to TNFi therapy as measured by DAS28, and depression often goes unrecognized by rheumatologists (2). Data in the current study could not be stratified by severity of depression. The current study also does not control for mental health interventions or treatments, but this may be a potential direction for future work. Many other

factors are likely to contribute to DMARD discontinuation but were not directly assessed here such as adverse reactions, medication intolerance, copayment costs, other socioeconomic dynamics, and clinical remission due to low disease activity, although the latter would seem unlikely given the relatively abbreviated median time to treatment discontinuation.

An additional limitation of retrospective analysis of electronic health record data is that it does not provide sufficient granular data regarding individual patient scenarios and reasons for DMARD discontinuation. While pharmacy data are good at

Table 5. Sensitivity analyses comparing the odds of low adherence (PDC < 80%) among treatment courses that persisted at least 6 months and 1 year

	MTX (n = 10 934) OR (95% CI)	TNFi (n = 5857) OR (95% CI)
Course length >6 months (fully adjusted)^a		
Psychiatric diagnosis (vs. none)		
Depression/anxiety	1.22 (1.11, 1.33) ^b	1.23 (1.09, 1.39) ^c
PTSD	1.15 (1.03, 1.30) ^d	1.22 (1.04, 1.42) ^d
	MTX (n = 8460) OR (95% CI)	TNFi (n = 4482) OR (95% CI)
Course length >1 year (fully adjusted)^a		
Psychiatric diagnosis (vs. none)		
Depression/anxiety	1.29 (1.16, 1.43) ^b	1.23 (1.07, 1.42) ^c
PTSD	1.19 (1.05, 1.36) ^c	1.33 (1.12, 1.59) ^c

Abbreviations: anti-CCP = anti-cyclic citrullinated peptide antibody; BMI = body mass index; CHF = congestive heart failure; CI = confidence interval; CRP = C-reactive protein; HCQ = hydroxychloroquine; LEF = leflunomide; MTX = methotrexate; OR = odds ratio; PDC = proportion of days covered; PTSD = posttraumatic stress disorder; RDCI = Rheumatic Disease Comorbidity Index; SSZ = sulfasalazine; TNFi = self-injectable tumor necrosis factor inhibitor.

^a Adjusted for calendar date, age, sex, race, BMI, RDCI, CRP, disease duration >5 years, ever anti-CCP positive, concurrent medication use (MTX, prednisone, TNFi, HCQ, SSZ, LEF), diabetes, hypertension, CHF, history of malignancy, current smoking. For TNFi, also adjusted for drug name and initial vs. subsequent biologic course.

^b $P < 0.001$.

^c $P < 0.01$.

^d $P < 0.05$.

estimating approximate medication usage, this may not be precisely reflective of actual patient medication-use patterns. For example, temporary discontinuations less than 90 days in length are not captured in our analysis of drug persistence. Also, given the potential stigma associated with psychiatric diagnoses, the true prevalence of PTSD, depression, and anxiety may not be fully captured by diagnosis codes alone. Another limitation of this study is that the patient population was overwhelmingly Caucasian and male, which suggests that this population may not be entirely generalizable to the national RA population. Lastly, dual care received from the VA and the civilian health care systems may result in prescriptions not captured by this analysis, but recent work suggests that this scenario is uncommon given that the vast majority of US veterans receive their RA care through the VA system (35).

This study is highlighted by several strengths. A large, nationwide cohort with over 23 000 initial courses of MTX and TNFi was examined. The VA electronic medical record provided extensive real-world data captured during clinical care, and the use of VA pharmacy records allowed for precise measurement of drug courses and discontinuations. This study is among the first to examine DMARD persistence in US veterans with RA and coexistent PTSD, depression, and anxiety. This is of particular importance given the high prevalence and morbidity of these conditions among the US veteran population.

In conclusion, PTSD, depression, and anxiety are associated with a greater likelihood of MTX and TNFi discontinuation

in US veterans with RA after adjusting for pertinent covariates. Poor adherence may play a role in this association; however, other underlying factors likely contribute and warrant further investigation.

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All authors contributed to drafting the article or revising it critically for important intellectual content, approved the final version to be published, and take responsibility for the integrity of the data and the accuracy of the data analysis.

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