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# Introduction and switching of biologic agents are associated with antidepressant and anxiolytic medication use: data on 42 815 real-world patients with inflammatory rheumatic disease

Vasiliki-Kalliopi Bournia,[1] Maria G Tektonidou,[1] Dimitrios Vassilopoulos,[1] Katerina Laskari,[1] Stylianos Panopoulos,[1] Kalliopi Fragiadaki,[1] Konstantinos Mathioudakis,[2] Anastasios Tsolakidis,[2] Panagiota Mitrou,[3] Petros P Sfikakis[1]

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For numbered affiliations see end of article.

**Correspondence to**
Vasiliki-Kalliopi Bournia; lily_bournia@hotmail.com and Petros P Sfikakis; psfikakis@med.uoa.gr

## ABSTRACT

**Objectives** Depression and anxiety are linked bi-directionally with inflammatory rheumatic diseases (IRDs) activity, which in turn, depends on subjective patient reported outcomes that can be distorted by comorbid mood disorders. We tested the hypothesis that introduction and/or switching of biologic agents for IRDs are associated with treatment for depression and/or anxiety, by analysing real-world data.

**Methods** Using a country-wide electronic prescription database (10 012 604 registered, 99% population coverage), we captured almost all patients with rheumatoid arthritis (n=12 002), psoriatic arthritis (n=5465) and ankylosing spondylitis (n=6423) who received biologic disease modifying anti-rheumatic drugs (bDMARDs) during a 2-year period (8/2016–7/2018). Concomitant antidepressant/anxiolytic medication use was documented in patients who started or switched bDMARDs and compared with those who remained on conventional synthetic (cs)DMARDs or the same bDMARD, respectively, by multivariate regression analysis.

**Results** Two-year data analysis on 42 815 patients revealed that bDMARD introduction was associated with both antidepressant [OR: 1.248, 95% CI 1.153 to 1.350, p<0.0001] and anxiolytic medication use [OR: 1.178, 95% CI 1.099 to 1.263, p<0.0001]. Moreover, bDMARD switching was also associated with antidepressant [OR: 1.502, 95% CI 1.370 to 1.646, p<0.0001] and anxiolytic medication use [OR: 1.161, 95% CI 1.067 to 1.264, p=0.001]. Notably, all these associations were independent of age, gender, underlying disease diagnosis and concomitant glucocorticoid or csDMARD medication use.

**Conclusion** In real-world settings, both introduction and switching of bDMARDs in patients with IRDs were associated with the presence of mood disorders. Although a causal relationship is uncertain, the impact of depression and anxiety should always be considered by physicians facing the decision to introduce or switch bDMARDs in patients with active IRDs.

## Key messages

### What is already known about this subject?

- Depression and anxiety are common in patients with inflammatory rheumatic diseases (IRDs) and may negatively affect patient outcomes.

### What does this study add?

- Analysis of data from 42 815 patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis who received bDMARDs and/or csDMARDs between 8/2016 and 7/2018 revealed that both initiation and switching of bDMARDs were associated with the use of antidepressant and anxiolytic medications, independently of age, gender, underlying disease and concomitant glucocorticoid or csDMARD use.

### How might this impact on clinical practice?

- Mood disorders that can either directly affect IRD activity and/or influence subjective patient-reported outcomes should be taken into account by rheumatologists who face the decision to initiate or switch bDMARDs.

## INTRODUCTION

Depression and anxiety are common in patients with inflammatory rheumatic diseases (IRDs) influencing disease activity, quality of life and patient outcomes.[1] The relationship between mood disorders and inflammation seems to be bi-directional, as chronic pain and inflammation are considered to be important mediators of depression, while at the same time depression affects perception of pain and reduces response to treatment, possibly by

minimising patient adherence to medication.[2] In addition, inflammatory disease activity assessment depends largely on subjective patient reported outcomes that can be severely distorted by comorbid mood disorders, thus affecting the physicians' decisions.

Biologic disease modifying anti-rheumatic drugs (bDMARDs) were introduced for the treatment of patients with rheumatoid arthritis (RA) in 1998 and have ever since revolutionised the treatment of patients with chronic non-infectious inflammatory diseases who do not respond adequately to conventional treatment.[3 4] Although there is an extensive literature on the interplay between inflammation and depression or anxiety, to the best of our knowledge, a possible association between the decision to initiate and/or switch bDMARDs for inflammatory arthritis and spondylitis and the presence of mood disorders has not been examined.

Herein, we had the opportunity to analyse big data on the use of bDMARDs for IRDs, derived from a country-wide electronic prescription database. Because the cost of bDMARDs is fully reimbursed by the national healthcare system, even for persons without insurance, all patients receiving these drugs among a country population of approximately 10 400 000 people are included in the database. An almost 100% population coverage and completeness of the data allowed us to test the hypothesis that introduction and/or switching of bDMARDs is associated with antidepressant and/or anxiolytic medication use in real-world patients with IRDs.

## PATIENTS AND METHODS

In this retrospective population-based study, the e-Government Centre for Social Security Services prescription database (IDIKA) was searched using prespecified ICD-10 codes to capture every patient with RA (ICD-10 codes: M05, M05.0, M05.1, M05.2, M05.3, M05.8, M05.9, M06, M06.2, M06.3, M06.4, M06.8, M06.9), psoriatic arthritis (PsA, ICD-10 codes: M07, M07.0, M07.1, M07.3, L40.5) and ankylosing spondylitis (AS, ICD-10 codes: M45, M46, M46.0, M46.1, M46.8, M46.9, M07.2) in Greece who had filled at least one prescription for bDMARDs [Adalimumab (ATC5: L04AB04), Certolizumab-pegol (L04AB05), Etanercept (L04AB01), Golimumab (L04AB06), Infliximab (L04AB02), Abatacept (L04AA24), Anakinra (L04AC03), Rituximab (L01XC02), Secukinumab (L04AC10), Tocilizumab (L04AC07), Ustekinumab (L04AC05)] between August 1, 2016 and July 31, 2018. All patients who had filled at least two prescriptions for conventional synthetic (cs)DMARDs [Methotrexate (L01BA01 and L04AX03 for subcutaneous and oral formulations, respectively), Leflunomide (L04AA13), Hydroxychloroquine (P01BA02), Sulfasalazine (A07EC01), Ciclosporin (L04AD01), Azathioprine (L04AX01), D-penicillamine (M01CC01)] during the same time period, were also included.

Patients with 'other arthritis' (M13, M13.0, M13.1, M13.8, M13.9), enthesopathies (M76.9, M77, M77.8), iridocyclitides (H20, H20.0, H20.1, H20.8, H20.9), arthropathy related to either Crohn's disease (M07.4) or ulcerative colitis (M07.5) and 'other enteropathic arthritis' (M07.6) were excluded from the study. Also, for those patients who had two or more of the above-mentioned ICD-10 diagnoses during the time period under study, only the more recent was taken into consideration for classification purposes.

The following data were recorded for all patients during the 2-year period: age at baseline, gender, use of bDMARDs, csDMARDs, glucocorticoids [betamethasone (H02AB01), methylprednisolone (H02AB04), prednisolone (H02AB06)], antidepressants [tricyclic antidepressants (N06AA), selective serotonin reuptake inhibitors (N06AB), non-selective monoamine oxidase inhibitors (N06AF), monoamine oxidase-a inhibitors (N06AG), other antidepressants (N06AX)] and anxiolytic medications [benzodiazepine derivatives (N05BA), Diphenylmethane derivatives (N05BB), Azaspirodecanedione derivatives (N05BE), Carbamates (N05BC), Dibenzobicyclo-octadiene derivatives (N05BD), Other anxiolytics (N05BX)].

Introduction of bDMARDs between 8/2016 and 7/2018 was documented for patients who had not filled a prior prescription for any bDMARD ever since records were being kept in the IDIKA database (January 2012). A switch was recorded every time a patient filled a prescription for a bDMARD with a different Anatomical Therapeutic Chemical Classification (ATC5) code from the directly preceding one, during the study time period. Discontinuation of bDMARDs was noted for patients who did not fill any bDMARD prescription after July 31, 2018.

Permission for use of anonymised data deposited in IDIKA was obtained from the Greek Ministry of Health following the approval of our formal request, according to the European legislation for General Data Protection Regulation (April 27, 2016) and the national laws (4600/2019, 4624/2019, 3892/10, 3418/2005). Due to regulations intended to protect trade secret, information on specific bDMARD prescription patterns, other than anti-tumour necrosis factor (TNF)/non-anti-TNF agents, cannot be shown.

Use of any antidepressant and/or anxiolytic drugs was compared between patients who initiated a bDMARD and those who remained on csDMARDs, as well as between patients who switched bDMARD and those who remained on the same bDMARD, using multivariate logistic regression analysis. The level of statistical significance was set at $p<0.05$. The SPSS statistical software package (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0.; IBM Corp., Armonk, New York) was used for all analyses.

## RESULTS

A total of 42 815 patients with IRDs among 10 012 604 persons registered in the database (0.43%, 99.5% population coverage), of whom 18 925 were only on csDMARDs, were

captured (table 1). A total of 23 890 patients with IRDs in Greece initiated or continued bDMARDs during the 2-year period. Methotrexate and anti-TNF agents were the most commonly used csDMARDs and bDMARDs, respectively, across all disease and age groups in our population-based cohort. Distribution of patients treated with bDMARDs between RA (n=12 002), PsA (n=5465) and AS (n=6423) and their demographics (table 1) were comparable to our previously published country-wide prescription data for the period between 1/6/2014 and 31/5/2015.[5]

The number of patients with IRD who initiated, switched or discontinued a bDMARD between 1/8/2016 and 31/7/2018, stratified by diagnosis (RA, PsA, AS), age and gender, are shown in table 2. The percentage of patients that switched from one bDMARD to another was higher among PsA (18%) vs RA (13%) and AS (13.5%) patients ($\chi^2$ test, p<0.0001), with women having more switches than men in all disease subgroups (RA group: 13.6% in females vs 10.2% in males, PsA group: 21.2% in females vs 14.3% in males, AS group: 50.5% in females vs 49.5% in males, $\chi^2$ test, p<0.0001 for all comparisons).

The mean age of patients switching from one bDMARD to another was lower compared with non-switchers in the PsA group (54.96±12.84 vs 56.20±13.12 years, Student's t-test, p=0.007), marginally so in the RA group (63.06 ±13.44 vs 63.80±14.02 years, Student's t-test, p=0.051) and did not differ significantly in the AS group (5079 ±12.88 vs 51.24±13.07 years, Student's t-test, p=0.351).

Table 3 shows the number of switches from one anti-TNF agent to another, or to a non-TNF bDMARD (abatacept, anakinra, rituximab, tocilizumab, secukinumab, ustekinumab) and vice-versa, in patients who filled bDMARD prescriptions for IRDs during the study period. Higher numbers of switches per patient were noted in RA (1.47) vs PsA (1.12) and AS (1.09).

Antidepressant and anxiolytic medication usage were documented in 24% and 43% of patients with RA, 19% and 36% of patients with PsA and in 16% and 30% of patients with AS, respectively. As shown in figures 1 and 2, anti-depressant and anxiolytic medication were more common among older patients in our cohort. Accordingly, after adjustment for age, gender, underlying disease and concomitant treatment with glucocorticoids, bDMARDs and csDMARDs, patients with AS had a higher probability [OR: 1.130, 95% CI 1.031 to 1.238, p=0.009], while patients with RA had a lower probability [OR: 0.880 95% CI 0.821 to 0.943, p<0.0001] to receive antidepressants compared with patients with PsA. Likewise, after adjustment for the same confounders, AS did not differ significantly from patients with PsA, whereas RA patients had a lower probability to use anxiolytics compared with patients with PsA [OR: 0.817, 95% CI 0.770 to 0.866, p<0.0001].

As also shown in the figures, antidepressant (figure 1) and anxiolytic (figure 2) usage were more frequent among all age and disease subgroups of patients who initiated bDMARDs compared with those who remained on csDMARDs, and in any age, or disease subgroup of patients who switched to bDMARDs, compared with those who remained on the same therapy (with some exceptions in the subgroup of patients aged <45 years, for both antidepressants and anxiolytics). Multivariate analysis adjusted for age, gender, underlying disease and concomitant treatment with glucocorticoids and csDMARDs revealed a positive, association between bDMARD introduction and usage of antidepressants [OR: 1.248, 95% CI 1.153 to 1.350, p<0.0001] or anxiolytics [OR: 1.178, 95% CI 1.099 to 1.263, p<0.0001]. Likewise, after correction for age, gender, underlying disease and concomitant treatment with glucocorticoids, csDMARDs and anti-TNF usage, multivariate analysis revealed a positive, independent association between bDMARD switching and antidepressant [OR: 1.502, 95% CI 1.370 to 1.646, p<0.0001] or anxiolytic medication usage [OR: 1.161, 95% CI 1.067 to 1.264, p=0.001].

## DISCUSSION

To the best of our knowledge, this is the first study to show a positive association between the use of medications for depression or anxiety and both introduction and switching of bDMARDs, in a large, real-world population of patients with IRDs. Notably, these associations were independent of age, gender, underlying disease and concomitant glucocorticoid or csDMARD use.

Given the complex and bi-directional relationship of mood disorders with IRDs, the observed association may have at least three explanations, which are not mutually exclusive.

First, it has been previously shown that increased pain and physical disability, subsequent loss of social roles and employment, as well as medication side effects at higher disease activity, may predispose to depression.[6] More severe inflammation corresponds to higher levels of circulating pro-inflammatory cytokines, which have been implicated in the pathogenesis of depression through a direct effect on brain structures known to contribute to the development of mood disorders.[2 6] In fact, a recent large-scale study from Sweden indicated that in RA, PsA and AS patients, use of antidepressants and benzodiazepine-related agents decreased directly or soon after introduction of bDMARDs or non-biologics, possibly due to a collateral attenuation of psychiatric symptoms by the anti-inflammatory medications.[7] The link between depression and inflammation is also supported by the fact that patients with major depressive disorder harbour increased levels of pro-inflammatory cytokines, such as TNF, interleukin (IL)-1β and IL-6, increased cytokine receptors, acute phase reactants, such as Creactive protein (CRP) and soluble adhesion molecules, both in the peripheral blood and in the cerebrospinal fluid. Interestingly, increased peripheral inflammatory markers were more common among anti-depressant non-responders compared with responders.[8] Furthermore, it is well

**Table 1** Country-wide data stratified by diagnosis and age on demographics and medication use, including switches, of real-world patients with inflammatory rheumatic disease who filled prescription for DMARDs between 8/2016 and 7/2018

| | | Rheumatoid arthritis (n=27 462) | | | Psoriatic arthritis (n=8469) | | | Ankylosing spondylitis (n=6883) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | <45 years (n=1933) | 45–65 years (n=10 317) | >65 years (n=15 212) | <45 years (n=1429) | 45–65 years (n=4499) | >65 years (n=2541) | <45 years (n=2145) | 45–65 years (n=3738) | >65 years (n=1000) |
| Female gender (%) | | 1576 (82) | 8513 (83) | 11 975 (79) | 702 (49) | 2422 (54) | 1404 (55) | 831 (39) | 1500 (40) | 376 (38) |
| csDMARDs | Methotrexate (%) | 1076 (56) | 6172 (60) | 8321 (55) | 688 (48) | 2474 (55) | 1436 (57) | 315 (15) | 804 (22) | 265 (27) |
| | Leflunomide (%) | 329 (17) | 3130 (30) | 5110 (34) | 129 (9) | 749 (17) | 522 (21) | 39 (2) | 131 (4) | 35 (4) |
| | Hydroxychloroquine (%) | 575 (30) | 2846 (28) | 3813 (25) | 31 (2) | 91 (2) | 57 (2) | 26 (1) | 74 (2) | 15 (2) |
| | Other csDMARDs (%) | 205 (11) | 703 (7) | 649 (4) | 382 (27) | 929 (21) | 366 (14) | 166 (8) | 292 (8) | 74 (7) |
| bDMARDs | Anti-TNF (%) | 934 (34) | 3697 (36) | 4230 (28) | 890 (62) | 2394 (53) | 1095 (43) | 1989 (93) | 3273 (88) | 872 (87) |
| | Non-anti-TNF (%) | 336 (17) | 1554 (15) | 2095 (14) | 338 (24) | 972 (22) | 409 (16) | 180 (8) | 410 (11) | 97 (10) |
| Glucocorticoids (%) | | 1073 (56) | 6262 (61) | 10 136 (67) | 472 (33) | 1544(34) | 1008 (40) | 376 (18) | 755 (20) | 271 (27) |
| Anxiolytics (%) | | 323 (17) | 3825 (37) | 7788(51) | 226 (16) | 1525 (34) | 1281 (50) | 309 (14) | 1240 (33) | 475 (48) |
| Antidepressants (%) | | 241 (12) | 2394 (23) | 3988 (26) | 143 (10) | 834 (19) | 591 (23) | 235 (11) | 673 (18) | 208 (21) |

bDMARD, biologic DMARD; cDMARD, conventional synthetic DMARD; DMARD, disease modifying anti-rheumatic drugs; TNF, tumour necrosis factor.

**Table 2** Country-wide data stratified by diagnosis, age and gender on patients who initiated, switched or discontinued (including deaths) any bDMARD, among all patients who filled at least one bDMARD prescription for inflammatory rheumatic disease between 8/2016 and 7/2018

| | | Rheumatoid arthritis (n=12 002) | | | Psoriatic arthritis (n=5465) | | | Ankylosing spondylitis (n=6423) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | <45 years (n=1185) | 45–65 years (n=4900) | >65 years (n=5917) | <45 years (n=1106) | 45–65 years (n=2994) | >65 years (n=1365) | <45 years (n=2060) | 45–65 years (n=3457) | >65 years (n=906) |
| Initiation | Male (%) | 83 (7) | 281 (6) | 310 (5) | 193 (17) | 370 (12) | 134 (10) | 406 (20) | 471 (14) | 119 (13) |
| | Female (%) | 347 (29) | 1240 (25) | 1246 (21) | 195 (18) | 514 (17) | 204 (15) | 348 (17) | 451 (13) | 84 (9) |
| Switching | Male (%) | 25 (2) | 101 (2) | 109 (2) | 95 (9) | 210 (7) | 76 (6) | 130 (6) | 232 (13) | 67 (7) |
| | Female (%) | 136 (11) | 569 (12) | 613 (10) | 108 (10) | 356 (12) | 132 (10) | 165 (8) | 215 (6) | 57 (6) |
| Discontinuation | Male (%) | 36 (3) | 141 (3) | 280 (5) | 43 (4) | 110 (4) | 105 (8) | 136 (7) | 219 (6) | 82 (9) |
| | Female (%) | 142 (12) | 590 (12) | 1013 (17) | 58 (5) | 188 (6) | 116 (8) | 140 (7) | 200 (6) | 58 (6) |

bDMARD, biologic disease modifying anti-rheumatic drugs.

**Table 3** Country-wide data stratified by diagnosis on bDMARD switches from an anti-TNF to a non-anti-TNF or to another anti-TNF and vice versa, in patients who filled bDMARD prescriptions for inflammatory rheumatic disease between 8/2016–7/2018

| bDMARD switches | Rheumatoid arthritis (n=2290) | Psoriatic arthritis (n=1097) | Ankylosing spondylitis (n=948) |
|---|---|---|---|
| From anti-TNF to non-anti-TNF (%) | 719 (31) | 448 (41) | 315 (33) |
| From one anti-TNF to another anti-TNF (%) | 738 (32) | 351 (32) | 514 (54) |
| From a non-anti-TNF to an anti-TNF (%) | 486 (21) | 167 (15) | 118 (12) |
| From non-anti-TNF to another non-anti-TNF (%) | 347 (15) | 131 (12) | 1 (0.1) |

Non-anti-TNF bDMARDs include: Abatacept, Anakinra, Rituximab, Tocilizumab, Secukinumab, Ustekinumab.
bDMARD, biologic disease modifying anti-rheumatic drugs; TNF, tumour necrosis factor.

known that patients who receive interferon-α therapeutically have a 15–40% risk to develop depression as a side effect, a rate significantly higher compared with untreated patients.[9] It has been postulated that interferon-α, a potent cytokine inducer, triggers mood disorders by heightening right amygdala emotional reactivity. Conversely, treatment with anti-TNF agents has been shown to induce remission of underlying depression in the context of systemic autoimmune diseases, possibly by decreasing right amygdala reactivity.[10] Other bDMARDs have also shown some effect in improving mental health in patients with systemic autoimmune diseases, with anti-IL6 therapy being the most effective.[11] It is therefore possible that either the increased activity of the underlying IRD, and/or the increased levels of inflammation, could account for the more frequent use of antidepressant and anxiolytic medications among patients initiating or switching biologic agents.

A second possible explanation for the observed associations could be the fact that depression per se may induce or aggravate IRDs.[12] In a longitudinal cohort of psoriasis patients followed up for 25 years, major depressive disorder was an independent risk factor for the development of PsA, with a HR of 1.37.[13] Furthermore, a significant association between major depressive disorder and subsequent development of RA has been shown in a cohort study from Taiwan [HR 1.65][14] and in a population-based cohort study from the UK [HR 1.38].[15] In the later study, the risk for RA development was found to be attenuated by the use of antidepressants.[15] In addition, a recent study showed that, according to patients' perception, psychological stress and mood disorders were the most frequent reasons underlying an RA flare.[16] Patients with depression have 1.76 times higher odds for medication non-adherence compared with non-depressed patients,[17] which could further account for the increased severity of co-morbid IRDs in this setting. Therefore, to the extent that depression can exacerbate IRDs, an association of antidepressant and anxiolytic medications with bDMARD initiation and switching can be anticipated.

A third explanation for the associations found between use of antidepressants or anxiolytics and the initiation or switching of bDMARDs in patients with IRD, could be that depression distorts subjective components of commonly used disease activity indices, thus misleading physicians to upscale treatment.[8 9] In a recent meta-analysis of patients with axial spondylarthritis reporting a 15% pooled prevalence of at least moderate depression, patients with depression displayed significantly worse disease activity (BASDAI, ASDAS) and functional impairment (BASFI, BASMI) indices compared with those without depression.

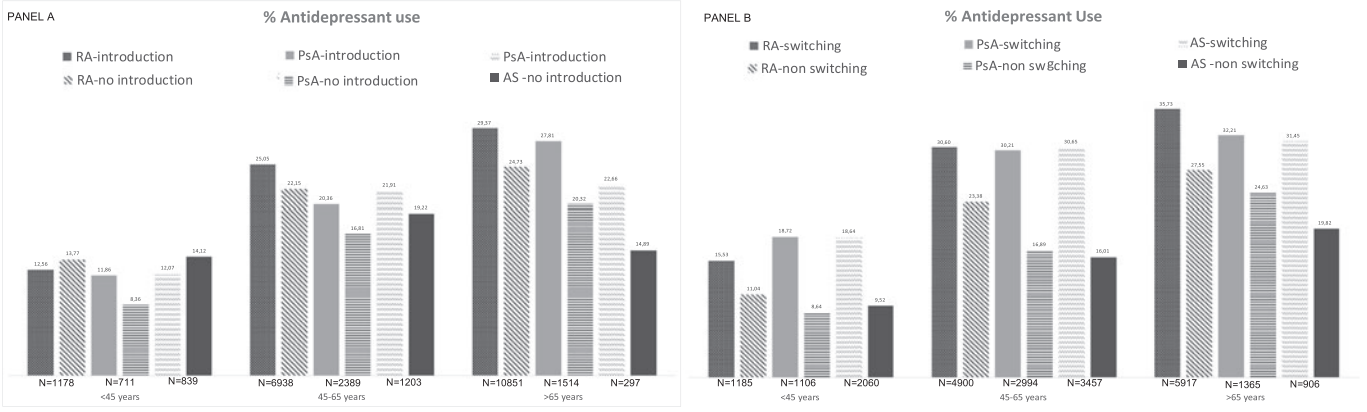


**Figure 1** Percentages of antidepressant medication use among real-world patients with inflammatory rheumatic disease, stratified by age, diagnosis and by introduction (panel A) or switching (panel B) of biologic disease modifying anti-rheumatic drugs (bDMARDs). N denotes patient numbers per disease/age groups.

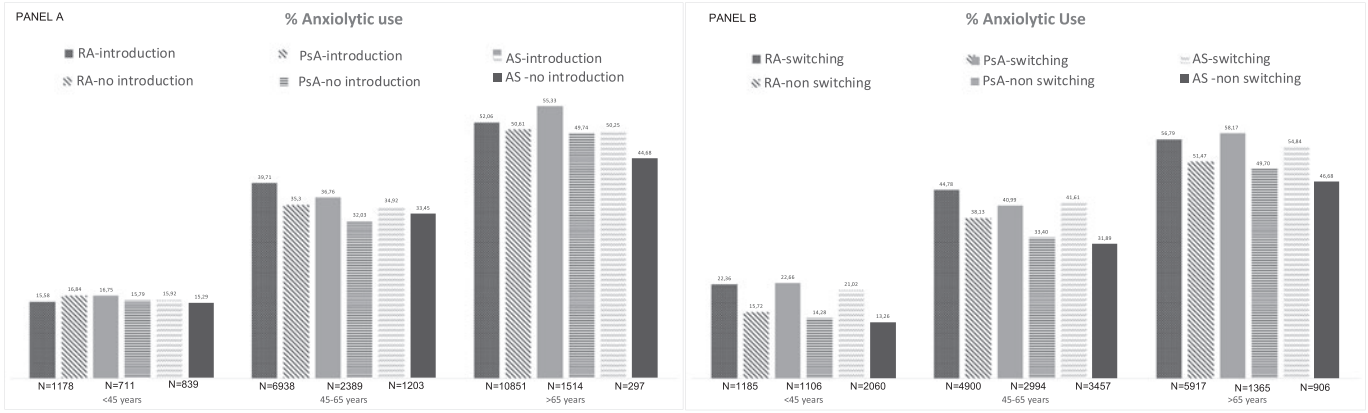


**Figure 2** Percentages of anxiolytic medication use among real-world patients with inflammatory rheumatic disease, stratified by age, diagnosis and by introduction (panel A) or switching (panel B) of biologic disease modifying anti-rheumatic drugs (bDMARDs). N denotes patient numbers per disease/age groups.

Although a causal effect of higher disease activity on depression cannot be excluded, it is also possible that depression distorted perception of pain in patients with axial spondylarthritis. In fact, the meta-analysis showed that differences in subjective indices (BASDAI, BASFI) were larger than differences in objective measures (BASMI, ASDAS), possibly indicating that patients with depression tended to overrate pain and discomfort caused by their underlying rheumatic disease and therefore overestimate disease severity.[10] Likewise, it has been shown that in patients with severe RA the patient visual analogue scale, one of the subjective components of DAS28, corelates with patients' beliefs regarding illness and treatment as well as with depression.[11] The influence of baseline depression and anxiety on the subjective components of DAS28 at 1-year follow-up is further supported by the results of a small study including 56 patients with RA, which showed that tender joint count and patient global assessment were the two DAS-28 parameters particularly affected by mood disorders.[9] Furthermore, in a prospective observational study including 1326 RA and 728 PsA patients, baseline depression or anxiety was associated with increased subjective measures of disease activity, such as patient's and physician's global assessment and with tender joint count and joint pain in RA at follow-up, but not with objective measures such as swollen joint count and acute phase reactants.[8]

In addition to the associations discussed above, the analysis presented herein revealed that higher rates of antidepressant medication usage occur in AS, followed by PsA patients, while RA patients had the lowest rates, after correction for age, gender, use of bDMARDs, csDMARDs and glucocorticoids, the latter of which may be per SE associated with mood disorders.[18] Likewise, patients with AS and PsA showed higher rates of anxiolytic usage compared with patients with RA. So far, meta-analyses and cohort studies have shown higher odds for depression among patients with RA, PsA and AS[19–22] compared with the general population. Depression in rheumatic diseases has been associated with impaired health-related quality of life,[23] worse response to treatment and lower improvement in disease activity over time.[8 12 24] Only few small cohort studies have directly compared the OR of depression between different IRDs, reporting an equal probability between patients with AS and RA [25] and a higher probability in patients with PsA compared with RA.[26] The higher burden of depression and anxiety among patients with AS and PsA compared with patients with RA found in our study conforms to some extent to the results of a recent study showing that disease burden as assessed by patient global assessment, pain and fatigue in PsA and AS was comparable to or greater than that in patients with RA.[27]

In our previous analysis of data from the country-wide prescription database between 06/2014 and 05/2015, more than 99% of patients with AS and PsA (combined group) received an anti-TNF agent, whereas only 0.78% used a non-anti-TNF bDMARD. In the current study, the rate of anti-TNF usage among bDMARD treated patients with AS and PsA has fallen to 88% and the use of non-anti-TNF bDMARDs has risen to 20%. The fact that other bDMARDs approved for the indications of AS and PsA, such as ustekinumab or secukinumab, only became available around 2016, could have precipitated switching from an anti-TNF agent to a non-TNF bDMARD in these patient groups during the time period we are studying. However, as shown in table 3, switching from one anti-TNF agent to another, still represents about 42% of the total switches recorded.

In the 2-year period between 1/8/2016 and 31/7/2018 several biosimilars of anti-TNF agents have been marketed and many physicians switched their patients to these new drugs in an effort to cut down on medical costs. To avoid recording switching to biosimilars as a switch to another bDMARD, we searched the database using ATC5 codes for all medications of interest, given that the ATC classification system relies

on substance and cannot discriminate between a bDMARD and its biosimilar.

Our study has several limitations. First, we were not able to capture all patients treated with csDMARDs in our country. The reason is that a significant number of patients with IRDs had no relevant prescription records kept in the electronic database system and as a result, have not been included in our cohort, because they prefer to pay the very low cost of methotrexate and hydroxychloroquine in order to avoid the time-consuming process of having them prescribed, which in addition costs more than the drug prices for those followed in private units. Second, we were unable to retrieve reliable individual-level data on IRD activity and patient functional impairment due to the structure of the e-Government Centre for Social Security Services prescription database. Although disability is a factor possibly predisposing to anxiety and depression, data on disease duration that could correlate with disability was also not available. Third, our findings did not rely on a psychiatric diagnosis of depression and anxiety, but the diagnosis of mood disorders was indirectly inferred from the use of antidepressant and/or anxiolytic medications. As a result, the lack of data on the possible concomitant presence of fibromyalgia for which antidepressants and anxiolytics are commonly prescribed may confound our results. On the other hand, not all patients with RA or PsA and concomitant depression use antidepressants,[20 28] therefore our approach has clearly missed some of them. Although a comparison of our findings with antidepressant and anxiolytic prescription patterns in a non-IRD population would be revealing, it would require data for which we have not requested access. Finally, our study examines the use of antidepressant and anxiolytic medications and associates them with the introduction and switching of bDMARDs in patients with IRD over the entire time span of the two-year period under study. Consequently, an exact temporal association of bDMARD introduction or switching with the use of psychiatric medications cannot be supported, mainly due to the lack of an index event (introduction or switching) in the control group.

A universal healthcare system with single-payer medication coverage and no out-of-pocket cost for bDMARDs, provides a unique opportunity to test our initial hypothesis on a population level, avoiding any selection bias. A major strength of our study is the fact that the database from which our cohort is derived covers almost the entire country's population, therefore practically all patients with RA, PsA and AS treated with bDMARDs in Greece. The large sample size allows for robust estimates of association, whereas current demographic findings are consistent with previous observations in the same real-world population.[5]

To conclude, depression and anxiety that are bi-directionally related with IRD, may contribute to bDMARD initiation and switching in these patients, either by aggravating disease severity and/or by distorting the perception of patient-reported outcome measures. Mood disorders should be always considered by practicing rheumatologists upon the decision to propose to an 'inadequately treated' patient the introduction or switching of a biologic agent. Whether the same holds true for patients with psoriasis and inflammatory bowel disease needs further investigation.

**Author affiliations**
[1]Joint Rheumatology Program, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[2]IDIKA SA - e-Government Center for Social Security Services, Athens, Greece
[3]Hellenic Republic Ministry of Health, Athens, Greece

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**ORCID iDs**
Vasiliki-Kalliopi Bournia http://orcid.org/0000-0002-2162-1362
Maria G Tektonidou http://orcid.org/0000-0003-2238-0975

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