

Major depressive episodes are associated with poor concordance with therapy in rheumatoid arthritis patients: the impact on disease outcomes

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Abstract

Objective

Our objective was to investigate associations between major depressive episodes (MDE), concordance with therapy (CwT) and disease outcomes in rheumatoid arthritis patients.

Methods

Seventy-eight outpatients receiving ≥ 1 disease modifying anti-rheumatic drug and without significant comorbidity had concomitant rheumatic and psychiatric evaluations. CwT was defined according to a questionnaire. MDE was defined using the Mini International Neuropsychiatric Interview and the severity of depressive symptoms was assessed with the Beck Depression Inventory (BDI-II). Appropriated statistic was used. IRB approval was obtained.

Results

Patients included (73 ♀) had (mean \pm SD) age of 44 \pm 10 years and (median, range) disease duration of 10 years (5.2–15.8).

Current MDE were diagnosed in 24 patients (30.8%); 60 patients (76.9%) were CwT. Patient-non-CwT were more frequently diagnosed with MDE and tend to have higher BDI scores. They had significantly more disease activity according to patient-pain VAS and swollen joint counts. Both groups were similar regarding demographic variables, treatment and comorbid conditions.

Forty-one patients (53%) had clinically important depressive symptoms (BDI \geq 10), among them 20 had mild depression, 14 moderate and 7 severe depression. Patient-non-CwT had more frequently moderate depression (according to BDI score) than their counterparts and similar tendency was found regarding severe depression. Patient-CwT who additionally had lower BDI scores had better disease outcomes than concordant patients with higher BDI scores. Similar results were found in non-CwT patients but statistical significance was limited to disease activity.

Conclusion

Prevalence of current MDE in RA patients was of 31%; those patients had poorer CwT and worse outcomes than mentally healthy patients.

Key words

major depressive disorder, rheumatoid arthritis, medication adherence, medication persistence, disease outcomes.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that may result in significant disability, morbidity and increased mortality (1-3). Earlier aggressive treatment with disease-modifying drugs (DMARDs) plays a major role in improving patient outcomes (4). However, poor concordance with therapy (CwT) is a substantial problem that affects 20% to 70% of the patients during follow-up (5-15). In addition, concordance with prescribed medication regimens (and placebo regimens) predicts better outcomes and collecting CwT data from patients is now considered as mandatory when performing clinical trials. By contrast, poor CwT contributes to substantial worsening of the disease, increased disease's flares and decreased rates of remission (11, 12, 15-17).

Depressive symptoms and syndromes are common findings in patients with chronic diseases. Their prevalence in RA patients ranges from 13 to 42% (18-25); variations depend on the methodology used to assess depression. Structured psychiatric interviews allow the diagnosis of psychiatric disorders according to international criteria and have been widely used for clinical assessment. Self administered questionnaires such as the Beck Depression Inventory (BDI) assess the subjective severity of depressive symptoms and are used for follow-up evaluations although they do not provide a diagnostic criterion. BDI has been validated to measure depression in Mexican RA patients (25). Depression is also associated with worse outcomes. RA patients with subsequent depression have increased health care service utilisation (24) and are more likely to discontinue anti-tumour necrosis factor alpha treatment (26) although this finding has not been replicated in RA patients on traditional DMARDs (27). In patients with RA, comorbid depression is an independent risk factor for incident myocardial infarction (28), suicidal ideation and death (29, 30).

Depression is frequent in RA patients and is associated with poor concordance with prescribed regimens in some rheumatic diseases. In addition, poor concordance with traditional DMARDs

is frequent in RA and affects disease's outcomes. We sought to examine the relationship between depression, CwT and disease outcomes in Mexican RA patients from a tertiary level care Centre.

Material and methods

Study design, sample size and study population

This was an observational and cross-sectional study performed at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a tertiary care and referral Centre for rheumatic diseases in México City.

A sample size of 78 RA ambulatory patients to be included was previously determined in order to achieve the study's objective. Over a 10 month period (April 2011-January 2012) RA outpatients were randomly invited to participate and after acceptance included in the study. Inclusion and exclusion criteria were assessed by chart review and verbal questioning of the potential participants prior to the study inclusion. More than 90% of the patients randomly selected accepted to participate. Eight patients denied and referred they had insufficient time for the psychiatric evaluation; they were substituted by the next consecutive randomised patient who agree to participate.

Inclusion criteria were outpatients with RA according to the American College of Rheumatology 1987 classification criteria (31), with current treatment with at least 1 DMARD. Exclusion criteria included patients with overlap syndrome and patients with any relevant medical or psychiatric condition but RA (see definition section). Rationale for exclusion criteria was to minimise the impact of comorbid conditions on patient's reported outcomes. Also, it may be stated that relevant comorbid conditions are medically treated and that more intensive treatments negatively impact medication adherence (16, 32).

Rheumatic evaluations

Rheumatic evaluations included a personal interview in order to confirm socio-demographic characteristics, co-morbid conditions and treatment received during the month prior to study entry (use

Competing interests: none declared.

of corticosteroids [yes/no], number of DMARDs/patient and number of other drugs/patient); chart review in order to assess disease characteristics and to confirm absence of relevant comorbid conditions; swollen and tender joint counts performed on 28 joints and a 0–100 mm physician-filled visual analogue scale (Ph-VAS) for overall disease activity; serum determinations of erythrocyte sedimentation rate (ESR) performed by Westergren method, of C-reactive protein (CRP) and of rheumatoid factor (RF) both performed by nephelometry, and of antibodies to cyclic citrullinated peptides (ACCP) performed by second generation ELISA. Before the physician evaluation, patients completed Spanish version of the Rheumatoid Arthritis Disease Activity Index (RADAI) (33), of the Medical Outcome Short Form 36 (SF-36) (34), of the Health Assessment Questionnaire (HAQ) (35), a pain-VAS, an overall-disease activity-VAS and a validated Spanish version of the BDI (25). Patients also filled the CQ, which is a 20-items questionnaire, formerly named as *compliance questionnaire* and renamed as *concordance questionnaire* according to the most recent recommendations (36). The CQ was locally designed in order to evaluate both, adherence to and persistence with medication; reproducibility of a first version applied to 20 randomly selected RA patients was of 0.8 (16). In the same study, performance of CQ for evaluating persistence on therapy was compared to that of serum determination of methotrexate; sensitivity, specificity, positive predictive value and negative predictive value of CQ were of 90.6%, 71.4%, 85.7% and of 80%, respectively (16).

Psychiatric interview

A psychiatric interview was performed in all instances by the same psychiatrist (NAC), soon after rheumatic assessment and on the same day. The psychiatrist was unaware of the information obtained by the rheumatologist. Sections from major depression disorder, dysthymia and suicidal risk of the validated Spanish version of the Mini International Neuropsychiatric Interview (M.I.N.I.) were applied (37).

Definitions

Relevant comorbidity was defined as a specific diagnosis requiring at least 3 related medical consultations within one year previous to the study entry, irrespective of a treatment indication. In addition, patients taking drug(s) for a specific diagnosis (but RA) although not recorded on the charts were considered to have relevant comorbidity.

Concordance with therapy

A patient was considered CwT if CQ-adherent and CQ-persistent.

A patient was considered to be *CQ-adherent* when boxes either 3 (“Almost always”) or 4 (“Always”) were filled from items 10 (“Since last visit, I took my medication exactly at the day/s indicated by my rheumatologist”), 11 (“Since last visit, I took my medication exactly at the day-times indicated by my rheumatologist”) and 12 (“Since last visit, every time I took my medication, I took the precise amount of tablets indicated by my rheumatologist”). A patient was considered to be *CQ-persistent* if in item 8 (“Since last visit, how often did you completely stop taking your medication?”) boxes 0 (“Never”) or 1 (“Almost never”) were filled (Appendix).

A major depressive episode was diagnosed according to the DSM-IV criteria using the M.I.N.I. (37, 38).

In addition, BDI-II was applied to assess the severity of depression symptoms (25). Clinically important depressive symptoms were considered if BDI ≥ 10 . The following cut-offs were considered: “mild depression” (10–18), “moderate depression (19–29) and “severe depression” (30–63), (25).

Ethics

The study was approved by local Institution Review Board. Written informed consent was obtained from all participating patients. Although all the scales and questionnaires were self-administered, a social worker was available in case assistance was needed.

A physician not involved in patient’s management met the social worker in charge of evaluating CwT in order to identify potential harmful behaviours (overdosing of medication).

All patients diagnosed with a mental disorder and requiring medical care were scheduled for specialised psychiatric care.

Statistical analysis

Medians and ranges or means and standard deviations were calculated for continuous variables and frequencies were determined for categorical variables. Description of variables was done according to their distribution as either median (ranges) of means (SD).

Chi square test was used for categorical variables. Student’s *t*-test and ANOVA tests were used to compare normally distributed variables and Mann-Whitney U and Kruskal-Wallis tests were used to compare non-normally distributed variables. Spearman correlation analysis was performed in order to investigate the relation between the severity of depressive symptoms and CwT, and outcomes.

Statistical significance was inferred at a level of $p \leq 0.05$. Receiver operating characteristic (ROC) curves were drawn to evaluate the ability of BDI to diagnosis current MDE. Analyses were performed using the SPSS/PC software (v.17.0; Chicago IL).

Results

Characteristics of the study population (Table I)

Seventy-eight patients were included, 73 (94%) female, middle-aged ([mean \pm SD] 43.8 \pm 10.1 years), with (mean \pm SD) 10.2 \pm 4 years of formal education. They had (median, range) 10.2 (5–15.3) years of disease duration and 72 patients had RF and ACCP (92.3%, each). Disease activity was mild at study entry as evaluated either per physician’s assessments or per patient’s assessments and (median, range) of swollen joint counts was 3 (1–8), of tender joint counts was 5 (2–10), of DAS28 was 4.3 (2.6–5.4), of ESR was 20 mm/H (8–33) and of CRP was 0.5 mg/dL (0.3–1.1). Patients had mild disability ([mean, range] HAQ was 1 [0–2]) and (mean, range) number of comorbidity/patient was 0 (0–1). Regarding treatment, 22 of them (28.2%) were receiving corticosteroids; (median, range) number of DMARDs/pa-

Table I. Comparison of patient-, disease- and treatment characteristics, and MDE (according to M.I.N.I.) and BDI scores between patients with CwT and their counterparts.

Variables	Whole population n=78	CwT Patients n=60	non-CwT Patients n=18	p-value
<i>Socio-demographics</i>				
Females, number (%)	73 (93.6)	55 (91.7)	18 (100)	0.58
Age at baseline, years (mean±SD)	43.8±10.1	44±10.3	42.3±9.5	0.64
Years of education (mean±SD)	10.2±4	9.8±4	11.3±2.4	0.12
<i>Disease characteristics</i>				
Disease duration, years*	10.2 (5-15.3)	9.8 (4.6-13.6)	12.9 (6.6-21.4)	0.87
Number of (%) patients with RF	72 (92.3)	55 (91.7)	17 (94.4)	1
Number of (%) patients with ACCP	72 (92.3)	55 (91.7)	17 (94.4)	1
<i>Disease activity and disability</i>				
RADAI (0-10)*	3 (1-5)	3 (1-5)	3.5 (1-6)	0.33
Patient- Pain-VAS (0-100)*	26 (8-50)	23 (3-50)	42 (12-79)	0.03
Patient-Overall-disease-VAS (0-100)*	27 (12-50)	23 (6-48)	27 (21-52)	0.10
Swollen joint count (0-28)*	5 (2-10)	5 (0-9)	6 (3-15)	0.05
Tender joint count (0-28)*	3 (1-8)	4 (0-8)	3 (2-8)	0.58
Physician-Overall disease-VAS*	19 (7-46)	19 (4-48)	18 (8-43)	0.60
DAS28*	4.3 (2.6-5.4)	4.3 (2.3-5.2)	5 (3.4-5.6)	0.11
Erythrocyte Sedimentation Rate, mm/H*	20 (8-33)	20 (8-33)	20 (8-51)	0.33
C-reactive protein, mg/dL*	0.5 (0.3-1.1)	0.5 (0.2-1)	0.7 (0.4-1.5)	0.10
Health Assessment Questionnaire (0-3)*	1 (0-2)	1 (0-1)	1.5 (0-2)	0.30
Short Form-36 (0-100)*	58 (43-75)	60 (44-76)	52 (37-73)	0.20
n° of Comorbidities/patient	0 (0-1)	0 (0-1)	0 (0-1)	0.33
<i>Current treatment</i>				
Corticosteroids use, number (%)	22 (28.2)	17 (28.3)	5 (27.8)	1
Number of DMARDs/patient*	2 (1-2)	2 (1-2)	2 (1-2)	0.17
Number of drugs for comorbidity/patient*	2 (1-2)	2 (1-2)	2 (1-2)	0.97
<i>Depression</i>				
Patients with actual MDE, number (%)	24 (33.8)	14 (23.3)	10 (55.6)	0.02
BDI score*	11 (3-20)	9 (3-16)	22 (2-26)	0.10

* mean (range)

RF: rheumatoid factor; ACCP: antibodies to cyclic citrullinated peptides; RADAI: Rheumatoid Arthritis Disease Activity Index; VAS: visual analogue scale; DAS28: Disease Activity Score (28 joints evaluated); DMARDs: disease-modifying anti-rheumatic drugs; CQ: Concordance questionnaire.

Table II. Comparison of BDI scores distribution between CwT patients and their counterparts.

Variables	Whole population n=78	CwT Patients n=60	non-CwT Patients n=18	p-value
n° (%) of patients with BDI scores ≤ 9	37 (47.4)	31 (51.7)	6 (33.3)	0.27
n° (%) of patients with BDI scores from 10 to 18	20 (25.6)	18 (30)	2 (11.1)	0.19
n° (%) of patients with BDI scores from 19 to 29	14 (17.9)	7 (11.7)	7 (38.9)	0.02
n° (%) of patients with BDI scores ≥ 30	7 (9)	4 (6.7)	3 (16.3)	0.41

BDI: Beck depression inventory; CwT: concordance with therapy.

tient was 2 (1-2), and number of other drugs/patient (it included NSAIDs, analgesics and calcium and D vitamin supplementation) was 2 (1-2). Most frequent DMARDs regimens were as follows: methotrexate monotherapy in 22 patients (28%), methotrexate combined with antimalarial in 19 (24%), methotrexate combined with antimalarial and sulfasalazine in 14 (18%) and methotrexate combined with sulfasalazine in

5 patients (6.4%). There were 6 additional DMARDs combinations which were used in 18 patients (23.6%). Finally, 60 patients (77%) were CwT (adherent and persistent).

MDE and BDI scores in the population and comparison between groups classified according to CwT

Current MDE was diagnosed in 24 patients (30.8%) after a structured inter-

view (M.I.N.I.). Depression was classified as unipolar in all the patients (none reported previous manic or hypomanic episodes) and 11 of the 24 MDE detected were single episodes (46%). Table I compares demographic, clinical, serological and treatment variables and MDE frequency between CwT patients and their counterparts. The formers had significantly less disease activity according to patient-pain VAS and swollen joint counts. Similar tendencies were found regarding disability evaluated as per HAQ and quality of life as per SF-36 which was found better in CwT patients. Also, CwT patients were less frequently diagnosed with MDE and tend to have lower BDI scores. Both groups of patients had similar treatment and (minor) comorbid conditions.

Patient's attributions for MDEs were investigated by direct assessment: 10 patients (41.7%) referred RA itself or RA deleterious outcomes (as pain, disability, etc...) as the main cause of their depressive symptoms, 11 (45.8%) patients identified interpersonal stressors and 3 patients (12.5%) referred no specific causation. Patients who referred RA itself or RA-related deleterious outcomes as the principal cause of their current MDE were compared to their counterparts regarding socio-demographic and disease characteristics, comorbidities, treatment and CwT; no differences were found but the formers received (median, range) higher number of DMARDs/patient: 2 (2-2.3) vs. 2 (1-2), p=0.03.

Severity of depressive symptoms based on the BDI in the whole population and comparison between patients classified according to CwT

A BDI cut-off ≥10 was considered for clinically important depressive symptoms. Forty-one patients (53%) had BDI≥10, distributed as follows: 20 patients (48.8%) had mild depression (BDI ≥10 and ≤18), 14 patients (34.2%) had moderate depression (BDI ≥19 and ≤29) and 7 patients (17.1%) had severe depression (BDI ≥30 to 63). Patient-non-CwT had more frequently moderate depression (according to BDI score) than their counterparts as shown

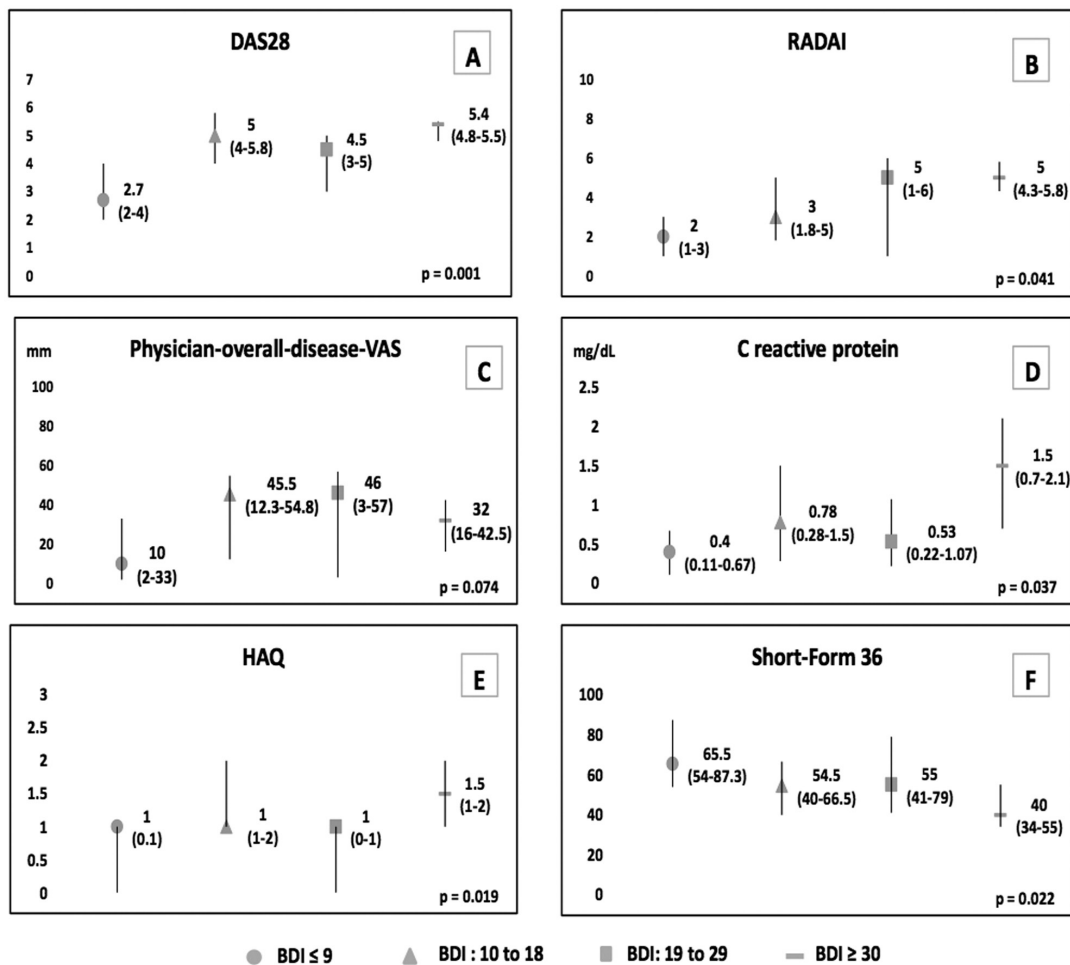


Fig. 1. RA outcomes in CwT patients classified according to BDI scores: **A:** DAS28; **B:** RADAI; **C:** physician-overall-disease-VAS; **D:** serum C reactive protein levels in mg/dL; **E:** HAQ; **F:** SF-36.

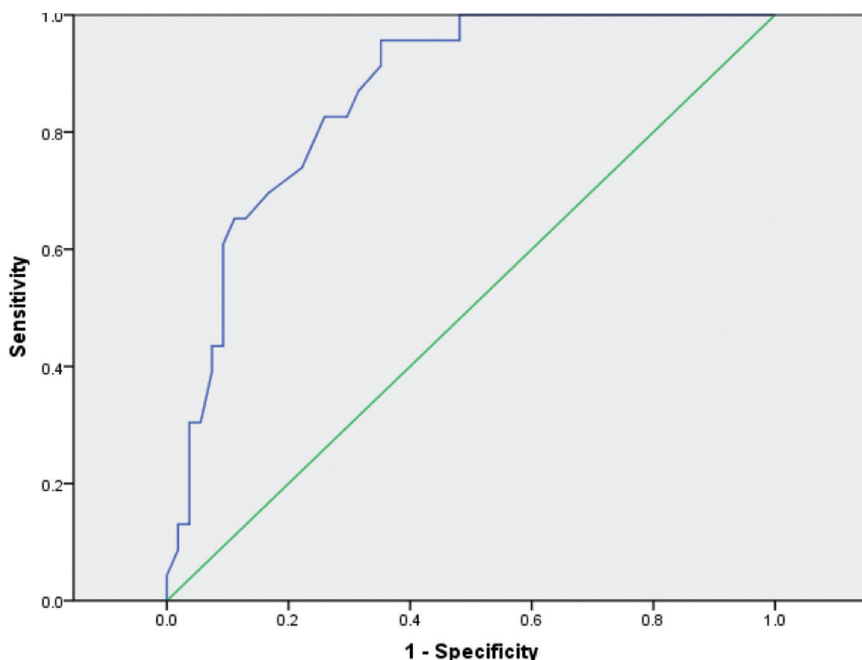


Fig. 2. ROC curve of local-BDI-cut-off in order to define MDE according to the M.I.N.I. Curve plots the relationship between sensitivity and 1-specificity for the local cut-off of the Beck depression inventory score to define patients with current major depressive episodes (MDE) according to the Mini international neuropsychiatric interview (M.I.N.I.).

in Table II, and tend to have more frequently severe depression.

We further explore the association between BDI scores and RA outcomes in patients classified by CwT. CwT patients who additionally had lower BDI scores also had significantly (but physician-VAS) lower disease activity (RADAI, pain-VAS, swollen and tender joint counts, ESR and CRP), lower disability (HAQ) and better health-related quality of life (SF-36) than CwT-patients with higher BDI scores as shown in Figure 1 ($p \leq 0.05$). Similar results were found in the 18 patients non-CwT but statistical significance was limited to (median, range) physician overall disease-VAS (BDI ≤ 9 [n=6]: 8 [8-12]; vs. BDI from 10 to 18 [n=2]: 34 [22-46]; vs. BDI from 19 to 29 [n=7]: 22 [11-43]; vs. BDI ≥ 30 [n=3]: 43 [41-76], $p=0.02$) and to tender joint counts (BDI ≤ 9 : 2 [1-3] vs. BDI from 10 to 18: 3 [3-3] vs. BDI from 19 to 29: 4 [3-10] vs. BDI ≥ 30 : 10 [7-11], $p=0.04$).

Mild but significant correlations were found between severity of depressive symptoms according to BDI cut-off and CwT ($\rho=-0.25$, $p=0.03$), and disease outcomes ($\rho=0.38$ to 0.49 , $p\leq 0.001$). Finally, the 24 patients with current MDE had (mean \pm SD) BDI score of 23.1 ± 10.6 , which was significantly greater than the BDI score from patients without MDE (vs. 8.7 ± 9.2 , $p=0.000$). Only 1 patient with current MDE had BDI score ≤ 9 . The remaining patients had BDI scores above 10 distributed as aforementioned (previously described).

ROC curves

We aimed to define the best local-BDI-cut-off in order to identify patients with current MDE according to the M.I.N.I. which was considered as the Gold Standard. The ROC curve of the data showed that the best cut-off was 19 (18.5) which corresponds to moderate/severe depression: sensitivity was 0.65, specificity was 0.89, positive predictive value was 0.71, negative predictive value was 0.14 and AUC was 0.86, 95% CI: 0.78–0.94 (Fig. 2).

In order to test consistency of the data, patients with moderate and severe depressive symptoms according to BDI ($\text{BDI}\geq 19$, $n=21$) were compared to the group conformed by patients with mild clinically important depressive symptoms and patients without clinically important depressive symptoms ($n=56$); the formers had greater clinical and serological disease activity, greater disability, lower health related quality of life and were less frequently concordant with therapy than their counterparts; socio-demographic variables, comorbidity and treatment were similar (data not shown).

Discussion

We performed a cross-sectional study and showed that up to 31% of RA patients had MDE when referred to a psychiatric evaluation. Depressive symptoms severity was most frequently mild although the whole spectrum of severity (mild, moderate and severe) was represented. Our prevalence figure for current MDE in RA patients is in accordance to published studies estimating the prevalence of depression in RA

patients from 13 to 45% (18-25, 39), although it is superior to the 20% figure believed to be the true prevalence of depression in RA when depression is assessed independently of disease-related items (40). In our study, we applied the BDI which includes 6 of them (41) to define the severity of depressive symptoms but current MDE was diagnosed according to a psychiatric interview; it has been suggested that simply eliminating somatically related items from an instrument may seriously affect its psychometric properties; in addition, using a standardised psychiatric interview minimises the impact of mistakenly rating physical symptoms as indicative of psychological disorder. Also, previous studies have shown that the highest risk for depression in RA occurs in persons who are middle aged or younger (21, 42). Most of our patients were under 45 years of age, which is in accordance to previous descriptions of RA populations from Latin-America (43) and could explain the higher prevalence of depression when compared to Caucasians patients. Finally, a recent study performed in Hispanic RA patients from USA showed a prevalence of significant depression of 32% (44). We found an association between presence of unrecognised MDE, poor concordance with therapy and worse disease outcomes. The study design do not allow any causal inference but we hypothesise that in RA patients, the negative effects of depression on disease outcomes are added to those of poor CwT on disease outcomes. It may be also hypothesise that unrecognised depression in RA patients directly affects concordance with therapy and both have additive effects on disease outcomes. Previous studies have confirmed that depression can increase disability, interfere with optimal treatment and result in poor CwT and misutilisation of health services (27-29, 45, 46). Particularly, it has been shown that RA patients who develop depression over follow-up are prone to biologics discontinuation (26, 47) but has not been confirmed in patients taking traditional DMARDs (47). We additionally found a strong association between increased BDI scores and worse disease outcomes

in patients with CwT. This finding was marginally reproduced in patients with non-CwT but we were limited due to the sample size (only 18 patients were non-CwT). In RA, poor medical adherence has also been associated to poor outcomes (11, 12, 15-17). This relationship has been generally defined as bidirectional, complex and probably not linear. Also, it has been suggested that it is not until patients reach certain levels of depression, that therapy behaviour and outcomes are affected.

Patients identified the disease itself and interpersonal stressors as the most frequent causes of their MDE. Interestingly, formers received a more intensive treatment with DMARDs when compared to their counterparts although no differences in CwT or other outcomes were found.

We finally identified the best local BDI cut-off for MDE as 19; it corresponds to the cut-off for moderate/severe depression (25) and performance of such BDI-cut-off to diagnosis current MDE was adequate. The M.I.N.I. was considered as the gold standard for the diagnosis of current MDE but it could be argued that it is impractical and expensive to have all RA outpatients been evaluated by a psychiatrist. Nonetheless, a differentiation between depressive symptoms and clinical depression is recommended and was made throughout this work. Our recommendation to assess depression in RA patients would be to "screen" patients first before subjecting them to a psychiatric interview and to use a validated scale for the population studied. In Mexican Mestizos patients the BDI is a validated tool (25).

The study has the following limitations. First, we did not evaluate anxiety, in addition to depression in our population. Recently, it has been shown that anxiety is more prevalent than depression and that it can elicit at least equally debilitating effects as depression (48). Second, we found that current MDE was associated to poor CwT and deleterious outcomes but could not delineate the direction of the association because of the cross sectional nature of our study. A longitudinal study would be helpful and is under development. Nonetheless, relationship between mental health dis-

orders, concordance with treatment and outcomes are not only complex but also bi-directional and subject to change. Third, our sample of RA patients may not be representative of RA seen in the community; however, recruitment of patients attending hospitals is viewed as an advantage when studying a clinical issue as depression (39). Furthermore, generalising findings to other populations such as RA patients living outside major cities should be done with caution due to the possible confounding effect of environmental stress. Fourth, In RA patients some covariates as levels of social stress and social support and disease's coping skills have also been associated with depression but were not investigated in our study (23, 48, 49). Finally, almost 10% of *a priori* elective and randomised RA patients denied participating; nonetheless, it has been stated that non-responders to general population's health surveys are not more reliable to positive or negative responding bias on measures of psychological well-being (50).

Conclusions

In conclusion, rheumatologists should be aware of the presence of depressive symptoms in RA patients as they are associated with both, poor concordance with DMARDs and poor outcomes. The BDI is easy to apply and to score, is inexpensive and can be incorporated to routine rheumatic evaluations. We additionally recommend that when scoring above 19, RA patients should be referred for a psychiatric interview as potential benefits may result in better disease outcomes.

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APPENDIX

Concordance Questionnaire (formerly Compliance Questionnaire)

Dear patient:

Medical treatments that help to control symptoms from diseases like yours are frequently indicated for a long period of time. Sometimes, patients forget or stop taking their medications, or missed a medical appointment which may account for less therapy effectiveness than previously expected.

We are interested in knowing possible reasons which may help you to continue taking your medication as prescribed in order to improve your medical attention.

Your participation in this study is voluntary. You may stop participating whenever you decide and if so, it will not interfere with the existing medical attention at the Institution.

You are invited to collaborate by answering the following survey.

This interview refers to the arthritis-therapy taking behaviour you had since last visit to the outpatient Early Arthritis Clinic.

Interview date: Day, Month, Year,

Name: First Last name, Second Last name, Name(s)

Institution identification number:

1.- Actual occupation

- | | | |
|-----------------------|---------------------------|-----------|
| 1 Housewife | 4 Non-officially employed | 6 Retired |
| 2 Student | 5 Unemployed | 7 Other |
| 3 Officially employed | | |

2.- Socioeconomic classification at the Institution

- | | | |
|----------------|----------------|----------------|
| 1 90% gratuity | 3 70% gratuity | 5 50% gratuity |
| 2 80% gratuity | 4 60% gratuity | 6 40% gratuity |

3.- Have you taken any alternative therapy, additionally to the treatment prescribed by the rheumatologist in charge of your care?

- 1 Yes 2 No If the answer is yes please specified which one.

4.- Since last visit to the Rheumatology outpatient clinic, did you stop taking the medication prescribed by your rheumatologist because of any reason including the choice of alternative medicine?

4. Always 3. Almost always 2. Sometimes 1. Almost never 0. Never

5.-Please rate in a scale from 0 to 10, how much you trust your rheumatologist.

0 indicates no trust at all and 10 indicates all the possible trust.

6.- Please rate in a scale from 0 to 10, how well you have understood treatment indications given by the rheumatologist in charge of your care.

0 indicates no understanding of medical indications regarding treatment and 10 indicates a perfect understanding.

7a.- Please rate in a scale from 0 to 10 the quality of the rheumatic evaluations you received. 0 indicates the poorest quality and number 10 the best quality.

7b.- Please rate in a scale from 0 to 10 the quality of central laboratory appointments you received.

0 indicates the poorest quality and number 10 the best quality (excellence).

8.- Since last visit to the Rheumatology outpatient clinic, how often did you completely stop taking your medication?

4. Always 3. Almost always. 2. Sometimes 1. Almost never 0. Never

**If you have answered numbers 4 (always), 3 (almost always), 2 (sometimes) or 1 (almost never), please answer the following question as well (question number 9).*

**If you have answered number 0 (never), please go to question number 10*

9.- Please read the following sentences and cross with an X each sentence you consider it was a reason to stop taking your medication during the past 2 months. You may choose more than one answer:

9.1- Because I had no money	Yes	No
9.2- Because it was not available at the drugstore	Yes	No
9.3- Because it does not make me feel better	Yes	No
9.4- Because it may me feel worse when I take it	Yes	No
9.5- Because the medication is very expensive	Yes	No
9.6- Because I forget to take it	Yes	No
9.7- Because nothing happens if I do not take it	Yes	No
9.8- Because I am taking a lot of medication at this time	Yes	No
9.9- Because I had to do more things than I usually do through the day	Yes	No
9.10- Because I did fewer things than I usually do through the day	Yes	No
9.11- Because nobody reminded me to take my medication	Yes	No
9.12- Because timing/s when my medication is prescribed is different from mealtime/s	Yes	No
9.13- Because I was not at home when I had to take my medication	Yes	No
9.14- Because I did not buy it	Yes	No
9.15- Because I went out on a trip	Yes	No

* If you wish to write some other reason/s, you may do it in the following space

10.- Since last visit to the Rheumatology outpatient clinic, I took my medication exactly at the day/s indicated by my rheumatologist

4. Always 3. Almost always. 2. Sometimes 1. Almost never 0. Never

11.- Since last visit to the Rheumatology outpatient clinic, I took my medication exactly at the day-times indicated by my rheumatologist

4. Always 3. Almost always. 2. Sometimes 1. Almost never 0. Never

12.- Since last visit to the Rheumatology outpatient clinic, every time I took my medication, I took the precise amount of tablets indicated by my rheumatologist

4. Always 3. Almost always. 2. Sometimes 1. Almost never 0. Never

13.- You consider that rheumatoid arthritis is

a) A chronic disease b) A disease that will resolve c) I do not know

14.- Do you have any confident to talk with? Yes No

15.- Do you consider that rheumatoid arthritis is a curable disease? Yes No I do not know

16.- If you have an economical urgency is there somebody who can help you? Yes No

17.- Do you consider that rheumatoid arthritis is an inherited disease? Yes No I don't know

18.- If you have doubts about your health, is there somebody trustworthy to talk with? Yes No

19.- Do you believe that someone who has rheumatoid arthritis should exercise? Yes No I don't know

20.- Do you have relatives to talk or spend time with them? Yes No

Items 1 and 2 are related to demography; items 3 and 4 are related to the use of alternative medicine (yes/no and modality); items 5 and 6 evaluate patient-physician relationship; in item 7 patients qualify the quality of physician's evaluation and central laboratory facilities; in item 8, patients use a Likert scale (0 to 4) to determine non-persistence on therapy; item 9 investigates patients reasons of inadequate medication taking behaviour and includes 15 predefined answers (most of them obtained from literature review) and one open answer; in items 10 to 12, patients use a Likert scale to evaluate adherence to DMARD therapy; items 13, 15, 17 and 19 investigate patient's knowledge about the disease (scored from 0 if no answer is correct to 4 if all the items are correctly answered); finally, items 14, 16, 18 y 20 determine the level of social support (scored from 0 to 4, if all the items are answered as Yes).