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Depression moderates the associations between beliefs about medicines and medication adherence in patients with rheumatoid arthritis: Cross-sectional study

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Abstract

The 'necessity–concerns framework' postulates that patients' adherence behaviour is influenced by beliefs about the necessity and the concerns patients have regarding their prescribed medicines. We hypothesized that depression moderates the associations between beliefs about medicines and medication adherence among people with rheumatoid arthritis. Using multivariate logistic regression, we observed that people experiencing more depressive symptoms showed stronger associations between necessity beliefs and adherence as well as attenuated associations between concerns and adherence, respectively, in a cross-sectional sample (N = 361). Thus, depression moderates the associations postulated in the 'necessity–concerns framework' in a differential way in people with rheumatoid arthritis.

Keywords

beliefs about medicines, depression, medication adherence, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that causes inflammation of the joints. It has a strong impact on people's everyday lives. Patients with RA suffer from pain, limited mobility and disability and experience a decreased quality of life (Matcham et al., 2014). The course of disease is chronic and often progressive. Current pharmacological treatment regimes can control the symptoms of RA and – when applied during early stages of the disease – have the potential to slow down the progression of the disease (Smolen and Aletaha, 2015). However, non-adherence to the prescribed medication is

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highly prevalent in RA, as in many other chronic conditions. According to a review conducted by van den Bemt et al. (2012), 30–80 per cent of patients with RA are not adherent. A large body of studies investigated the factors which could potentially influence medication adherence in RA. Two reviews have revealed that neither sociodemographic nor disease- or therapy-related factors were consistently associated with medication adherence, rather psychosocial factors were considered as crucial (Vangeli et al., 2015; van den Bemt et al., 2012).

There are various theoretical models which seek to describe and explain medication non-adherence with a focus on psychological constructs. The 'necessity–concerns framework' (Horne and Weinman, 1999) suggests that patients' adherence behaviour depends on the perceived necessity of medicines and on the concerns patients might have regarding their medication. It has been shown that these beliefs about medicines are associated with patients' extent of medication adherence. A systematic review and meta-analysis conducted by Horne et al. (2013) demonstrated that stronger beliefs about the necessity of medicines were associated with higher medication adherence and stronger concerns regarding medicines with lower adherence among patients with chronic conditions. Studies have demonstrated these associations also for patients with RA (De Thurah et al., 2010; Neame and Hammond, 2005; Nestoriuc et al., 2010; Spruill et al., 2014; Treharne et al., 2004; van den Bemt et al., 2009; Zwikker et al., 2014). However, little is known as to whether the strength of the observed associations between beliefs about medicines and adherence varies with patients' characteristics, that is, whether the associations are moderated by third factors such as comorbidities. This knowledge about how patients' characteristics could moderate the associations between beliefs about medicines and medication adherence seems crucial when developing and targeting future interventions.

One very common comorbidity in RA is depression. A major depressive disorder according to established diagnostic criteria is prevalent in about 17 per cent of patients with RA (Matcham et al., 2013). Self-reported depressive symptoms are even more prevalent (Dougados et al., 2014; Matcham et al., 2013). The presence of depression can alter the course of RA negatively via cognitive-behavioural or inflammatory pathways: patients with concurrent depression suffer from more pain, show a heightened disease activity (Rathbun et al., 2013) as well as generally poorer health outcomes (Morris et al., 2011). Some specific characteristics of people suffering from depression, such as negatively biased (social) cognitions or motivational deficits, can affect behaviours and the way in which cognitions shape behaviours (Weightman et al., 2014; Wisco and Nolen-Hoeksema, 2010). This suggests consequences for adherence behaviours: DiMatteo et al. (2000) analysed the relationship between depression and adherence to various treatment regimes and found depression to contribute to medication non-adherence among patients with different medical conditions. This has also been shown for patients with RA (Cabrera-Marroquin et al., 2014), even if a systematic review on depression and treatment discontinuation among patients with RA found the existing results to be inconclusive (Rathbun et al., 2013). In order to foster the understanding of medication adherence in RA and the applicability of the 'necessity–concerns framework', the investigation of the role of depression seems to be a key issue.

Therefore, the aim of this study was to analyse whether depression moderates the association between beliefs about medicines and medication adherence in patients with RA. It was hypothesized that the postulated associations (stronger necessity beliefs and higher adherence, weaker concerns and higher adherence) would be attenuated with higher depression scores.

Methods

This cross-sectional study is part of a longitudinal study on medication adherence in patients suffering from RA. The study was conducted at the Department of Rheumatology, Asklepios

Medical Center Bad Abbach, a tertiary care centre for patients with autoimmune and rheumatic diseases, located in the south of Germany.

Patients and recruitment

Patients were eligible for participation in the study if they were aged 18 years or older, had physician-diagnosed RA and were currently under medical treatment for RA. They were approached during an inpatient hospital stay or an outpatient visit and asked to provide informed consent for participation in the study. Recruitment took place over the course of 14 months. Patients were excluded from the study if they were aged less than 18 years, if they had a psychiatric diagnosis other than affective disorders or if they were unable to understand German. Finally, 361 patients with RA were included. The study has been approved by the ethics committee of University of Regensburg (file-number: 12-101-0126).

Measures and data collection

All participating patients were asked to complete self-report questionnaires. Additional information was extracted from patients' (electronic) health records.

Medication adherence was assessed using the 'Medication Adherence Report Scale' (MARS; German version: Mahler et al., 2010). It comprises five items on intentional and non-intentional adherence behaviours. Each item is scored on a 5-point Likert scale ranging from '1 = *never*' to '5 = *always*'. A sum score was calculated. In our sample, the resulting distribution was highly positively skewed; thus, we dichotomized the MARS score with values lower than 25 indicating non-adherence or incomplete adherence and the value 25 indicating complete adherence. The dichotomization with this cut-off score was used for all analyses presented in this article. Additionally, we performed sensitivity analyses using other cut-off values ($\geqslant$23; $\geqslant$24) (data not shown). This strategy was applied as there is no agreement in the literature on a cut-off value when dichotomizing the MARS, and sensitivity analyses can help assuring the robustness of findings.

Patients' beliefs about medicines were measured using two scales of the 'Beliefs about Medicines Questionnaire' (BMQ; Horne et al., 1999; German version: Mahler et al., 2012). The scale 'necessity' consists of five items assessing patients perceived necessity regarding their prescribed medicines (e.g. 'I could not live without my medicines'), the scale 'concerns' comprises six items on patients' concerns about their medicines (e.g. 'Sometimes I worry about my medicines'). All items are scored on a 5-point Likert scale (ranging from 'I strongly agree' to 'I strongly disagree'). Scale values are calculated as means with higher values indicating stronger beliefs.

The depression scale of the 'Hospital Anxiety and Depression Scale' (HADS; Zigmond and Snaith, 1983) was used to screen for symptoms of depression. The sum score ranges from 0 to 21, with higher values indicating the presence of more depressive symptoms. Different thresholds have been proposed for the HADS. We used the conventional cut-offs of 8+ (indicating a probable depression) and 11+ (indicating depression) (Zigmond and Snaith, 1983).

Data on current medication were obtained from patients' health records. All prescribed medications were assessed and categorized according to type of medication (non-steroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, disease-modifying antirheumatic drugs (DMARDs), biologicals and non-RA medication).

The '28-joint Disease Activity Score' (DAS28) was used to assess disease severity (Wells et al., 2009). It combines clinical (e.g. number of affected joints) and laboratory (C-reactive protein (CRP)) parameters with patients' perception of disease severity during the course of the past 7 days. The scoring was performed according to the published algorithms with higher values indicating higher disease activity.

Information on patients' sociodemographic background was obtained by questionnaire. The items captured sex, age, educational background,

migration background and living situation. Additional items referred to disease characteristics: age at time of diagnosis, distance to the provider of RA treatment and the experience of severe side effects due to RA medication.

Both data gathered by questionnaires from patients and data on current medication extracted from health records were entered twice and cross-checked in order to assure data quality.

Statistics

Descriptive statistics were calculated using frequencies and percentages or means (M) and standard deviations (SD). Group differences were determined by t tests or χ^2 tests.

In order to test whether depression moderates the association between beliefs about medicines and medication adherence, multivariate logistic regression analyses were computed for both the 'necessity' and the 'concerns' subscale, each including an interaction term with depression. This approach refers to a multiplicative interaction model. Predictor variables were transformed by grand mean centring. If the interaction term was significant, simple slope analyses were conducted with slopes for each the mean value, the mean value plus 1 SD and the mean value minus 1 SD of the moderator variable.

A large number of theoretically selected variables were investigated for inclusion as potential confounders of the association between necessity/concerns and adherence by means of univariate analyses with an entry p value of .20. Sex, the number of prescribed RA medicines and self-rated pain were found to be associated with both necessity beliefs and medication adherence in univariate analyses. Only the number of prescribed RA medicines and self-rated pain were associated with both concerns and medication adherence. These variables were thus included as potential confounders in the respective analyses.

Collinearity diagnostics were performed for both regression models. For both models, there was no indication for multicollinearity according to the variance inflation factors (VIFs), tolerance values and eigenvalues. Thus, all variables could be included simultaneously.

Results of the logistic regression analyses are given as odds ratios (OR) and 95% confidence intervals (CI). Model fit is reported by Nagelkerke's R^2.

p values <.05 were interpreted as statistically significant. All analyses were performed using SPSS.22, the moderation analyses were performed using the PROCESS macro for SPSS (Hayes, 2012).

Results

Sample characteristics

Patients' sociodemographic and disease-related characteristics are displayed in Table 1. A total of 361 patients with physician-diagnosed RA were included in the study, of which about 30 per cent were male. On average, patients were aged 60 years, and RA had been diagnosed approximately 11 years ago. The mean number of prescribed medicines was seven, including on average four prescribed RA medicines. In all, 43 per cent of participants reported that they had at least once experienced severe side effects due to their medication. About one-third of participants showed elevated depression scores, indicating a probable depression.

Bivariate analyses

In all, 32 per cent of patients were completely adherent. Patients' characteristics stratified according to being adherent or non-adherent are displayed in Table 1. There were significantly fewer men in the group of adherent patients (20% compared to 36% in the group of non-adherent patients, p = .002). Mean HADS-D scores were significantly lower among adherent patients than among non-adherent patients (p = .001). There were no statistically significant group differences in any other patient, disease or treatment-related variables.

Overall, patients held strong beliefs about the necessity of medicines and reported only

Table 1. Patient and disease characteristics, stratified for medication adherence.

	All (*N* = 361)	Adherent (*N* = 112)	Non-adherent (*N* = 239)
Male (%)	30.5	19.6	36.0*
Age (years) (*M*; SD)	60.20 (13.36)	60.31 (13.16)	59.80 (13.32)
Migrational background (%)	7.2	8.9	6.7
Schooling ⩾10 years (%)	39.4	41.8	38.2
BMI (*M*; SD)	27.75 (5.80)	28.20 (6.22)	27.61 (5.62)
Age at diagnosis (years) (*M*; SD)	49.26 (15.21)	48.35 (14.74)	49.31 (15.35)
Duration of disease (years) (*M*; SD)	10.94 (9.22)	11.35 (8.89)	10.82 (9.39)
Inpatient treatment (%)	21.7	18.0	22.6
Distance to provider of RA treatment (km) *M*; SD)	58.59 (44.75)	59.25 (46.03)	58.24 (44.58)
Experience of severe side effects (% yes)	43.2	39.3	45.2
Number of prescribed medicines (*M*; SD)	7.13 (3.68)	7.44 (3.80)	6.98 (3.62)
Number of prescribed RA medicines (*M*; SD)	3.86 (1.60)	4.12 (1.51)	3.77 (1.64)
NSAR (any, %)	16.4	17.1	16.3
Opioids (any, %)	14.4	13.5	15.1
Corticosteroids (any, %)	71.9	75.7	70.3
DMARDs (any, %)	75.8	79.3	74.1
Biologicals (any, %)	29.2	27.9	30.5
Self-rated pain (1-10; *M*; SD)	4.47 (2.78)	4.62 (2.75)	4.15 (2.84)
DAS28 (*M*; SD)	3.07 (1.57)	3.00 (1.68)	3.08 (1.53)
HADS depression (*M*; SD)	6.02 (3.83)	5.01 (3.99)	6.41 (3.62)*
BMQ necessity (*M*; SD)	4.27 (0.64)	4.36 (0.57)	4.23 (0.65)
BMQ concerns (*M*; SD)	2.84 (0.80)	2.60 (0.84)	2.94 (0.75)*

Group differences were analysed using χ^2 or t-tests.
M: mean; SD: standard deviation; RA: rheumatoid arthritis BMI: body mass index; NSAR: non-steroidal anti-inflammatory drug; DMARDs: disease-modifying antirheumatic drugs; DAS28: Disease Activity Score 28; HADS: Hospital Anxiety and Depression Scale; BMQ: Beliefs about Medicines Questionnaire.
*$p < .05$.

minor concerns. Bivariate analyses showed that adherent patients had higher scores on the necessity scale than non-adherent patients ($M = 4.36$ (SD = 0.57) vs $M = 4.23$ (SD = 0.65)). However, the difference was not significant. Adherent patients had significantly lower scores on the concerns scale ($M = 2.60$ (SD = 0.84) vs $M = 2.94$ (SD =0 .75); $p < .001$).

Moderation analyses

Results from logistic regression analyses are presented in Tables 2 and 3.

Necessity beliefs and depression were each significantly associated with medication adherence, with stronger necessity beliefs increasing (OR = 1.72; 95% CI: 1.08–2.74) and with higher depression scores decreasing the chance of being adherent (OR = 0.87; 95% CI: 0.81–0.94) (see Table 2). The interaction term 'depression × necessity' was also significant (OR = 1.15; 95% CI: 1.02–1.29). Slope analyses showed that the direction of the interaction was contrary to the postulated hypothesis: At the mean value of depression and 1 SD above, there were significant positive associations between necessity beliefs and adherence. However, when the depression score was low (mean minus 1 SD), there was no such association. This moderation effect of depression is illustrated in Figure 1(a).

The logistic regression analysis of medication adherence on *concerns* showed no significant association of concerns (OR = 0.74; 95% CI: 0.52–1.06), but the associations of depression

Table 2. Moderation analysis of medication adherence on depression and necessity.

	OR	95% CI	*p*
HADS depression	0.87	0.81; 0.94	.001
BMQ necessity	1.72	1.08; 2.74	.022
Interaction: depression × necessity	1.15	1.02; 1.29	.025

OR: odds ratio; CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; BMQ: Beliefs about Medicines Questionnaire.
Logistic regression analysis of medication adherence (Medication Adherence Report Scale (MARS)); predictors were mean centred; adjusted for sex, number of prescribed rheumatoid arthritis (RA) medicines, self-rated pain.
Nagelkerke's R^2 = .13.

Table 3. Moderation analysis of medication adherence on depression and concerns.

	OR	95% CI	*p*
HADS depression	0.91	0.84; 0.98	.020
BMQ concerns	0.74	0.52; 1.06	.104
Interaction: depression × concerns	1.08	1.01; 1.16	.030

OR: odds ratio; CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; BMQ: Beliefs about Medicines Questionnaire.
Logistic regression analysis of medication adherence (Medication Adherence Report Scale (MARS)); predictors were mean centred; adjusted for number of prescribed rheumatoid arthritis (RA) medicines, self-rated pain.
Nagelkerke's R^2 = .14.

with medication adherence (OR = 0.91; 95% CI: 0.84–0.98) and the interaction term 'depression × concerns' (OR = 1.08; 95% CI: 1.01–1.16) reached statistical significance. Simple slope analysis revealed that only in patients with low depression scores (mean minus 1 SD), concerns were negatively associated with medication adherence, while there was no significant association between concerns and adherence among patients with mean and high depression scores (see Figure 1(b)). These results are in line with our hypothesis.

Sensitivity analyses were performed with two additional cut-off values to dichotomize the MARS score (data not shown). The use of these cut-off values resulted in higher proportions of patients classified as being adherent (MARS ⩾ 24: 57.0% and MARS ⩾ 23: 70%). Moderation analyses showed that none of the associations were altered in their direction, although some did not reach statistical significance.

Discussion

Our study demonstrated that the presence of depressive symptoms moderates the relationship between beliefs about medicines and medication adherence in patients with RA. The findings imply that depression can alter the way in which beliefs about medicines translate into adherence behaviour. However, the results of this study did not support the hypotheses on the direction of the effects we had formulated. We had a priori hypothesized that depression would attenuate the associations between beliefs about medicines and medication adherence, but this was only true for the association between concerns and adherence. Regarding patients' perceived necessity – contrary to our hypothesis – depression was found to strengthen the association. This finding of a differential effect of depression warrants thorough discussion.

In this sample, patients generally hold strong beliefs about the necessity of their medicines and had less pronounced concerns. This is in line with results of other studies among patients with RA (Nestoriuc et al., 2010; van den Bemt et al., 2009; Zwikker et al., 2014) and could reflect specifics of the disease, such as the severity and the impact on participants' daily lives.

The negative relationship between concerns and medication adherence was attenuated in patients with moderate depression scores and not existing in patients with high depression scores. As hypothesized, the presence of depression may hinder the translation of beliefs into behaviours, thus reducing negative impact of potential concerns on adherence or making them obsolete. Possible explanations refer to characteristics of people with depression, such as indifference to beliefs and behaviours which are stable, rigid and not prone to change (Meiran et al., 2011).

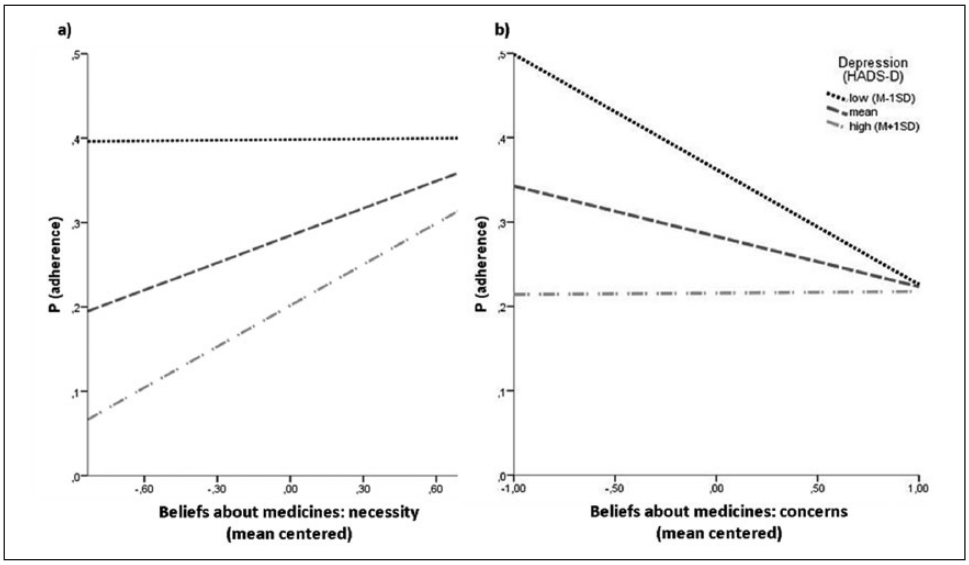

Figure 1. Depression as moderator of the association between necessity (a)/ concerns (b) and adherence.

Simple slopes equations of the regression necessity/concerns and medication adherence at three levels of depression. Medication adherence is expressed as the probability (*p*) of complete adherence (MARS = 25).

However, due to the findings on the role of depression for the association between beliefs about necessity of medicines and medication adherence, these assumptions about the underlying causes cannot be upheld: the association of necessity beliefs and adherence was basically attributable to persons with moderate or high depression scores, whereas there was no association in people with low depression scores. This finding suggests that necessity beliefs are crucial for adherence in patients who experience depressive symptoms, but only in them. There are two possible explanations: one could refer to depressive patients' motivational difficulties in engaging in behaviours that are not perceived as absolutely necessary or urgent. While people without depressive symptoms might have succeeded in behaving adherently even if necessity beliefs were low, people with depression might be reliant on the perception of high necessity for successfully implementing a behaviour. Another reason might be that during depressive episodes, people experience a heightened susceptibility for negatively connotated attitudes and negatively framed expectancies which have impact on the manifestation of non-adherent behaviours. (Low scores on the necessity scale stem from refusals to statements such as 'My medicines protect me from becoming worse' or 'My health in the future will depend on my medicines'.)

However, both explanations contradict the idea our initial hypothesis was built upon, that is, the attenuation of the relationship between necessity beliefs and medication adherence by depression due to the non-translation of attitudes into behaviours among people with depressive symptoms.

Instead, explanations for the differential effect of moderation by depression are needed. First, there may be common underlying constructs which manifest in high concerns about medications and high depression scores, such as negative affectivity or anxiety. Therefore, we did find some empirical overlap between the 'concerns' and the 'depression' scales, but this did not result in any negative impact on regression modelling. Assuming that depression and strong concerns frequently co-occur, there might be only low variance in depressive people's concerns regarding their medicines. This

could explain the attenuated association between concerns and medication adherence among people with depression.

Second, among people without depression, strong beliefs about the necessity of medicines held by them may have hindered the association between necessity beliefs and medication adherence becoming salient. At the same time, necessity beliefs that vary more strongly among people with depression could have been the prerequisite for the emergence of the association with medication adherence.

Third, when comparing the associations 'necessity–adherence' and 'concerns–adherence', one must consider that these two BMQ scales did not only cover different types of beliefs but also beliefs of positive ('necessity') and negative ('concerns') valence. It has been argued that opposite valences are associated with distinct motivational and behavioural pathways and that the (non-)correspondence in valences of attitudinal measures and behaviours can impact the size of their relationships (Richetin et al., 2011).

To the best of our knowledge, the 'necessity–concerns framework', that is, the prediction of adherence by beliefs about medicines, has not yet been investigated with focus on the potential moderating role of depression (or of another psychosocial variable). Regarding samples of patients with RA, only two studies have been performed on the 'necessity–concerns framework' which even explored depression, albeit it was accounted for only as a covariate. Zwikker et al. (2014) assessed the HADS score in their sample. They found that when including the HADS score (and other psychological variables) as covariates, the relationship between beliefs about medicines and medication adherence remained nearly unchanged. Unfortunately, they only used the overall score of the HADS, which combines symptoms of anxiety and depression, and thus, results of the study can hardly be compared with ours. Nestoriuc et al. (2010) investigated the effects of beliefs about medicines on self-reported side effects and also found depression not to contribute to the prediction of side effects by beliefs about medicines.

We consider the analysis of depression as a moderator for the association of beliefs about medicines and medication adherence worthwhile as it goes along with implications for both patient care and research: Depression is a very common comorbidity, not only of RA, but of many chronic conditions. It has been postulated to develop interventions based on the 'necessity–concerns framework' which address beliefs that hinder adherent behaviour. Some recent research projects have already engaged in the development of this kind of interventional measures for patients with RA (Zwikker et al., 2012). With regard to our findings, it might be crucial to specifically target patients with concurrent depression within the population of RA patients as the way in which beliefs about medicines impact on adherence behaviour could be altered among those patients. The findings of this study would suggest emphasizing the role of necessity beliefs among RA patient with concurrent depression. Embracing a broader perspective, we propose further work which helps disentangling the associations within the 'necessity–concerns framework'. If depression emerged as a crucial factor in various studies and across different patient populations, one could consider modifying or expanding the framework in order to increase applicability and validity.

Limitations

This study has some limitations. First, the results reported here are cross-sectional associations, and no conclusions on causality can be drawn.

Second, we had to rely on self-report measures of medication adherence and depression. Patients' medical records which are held in hospitals cover only data on prescribed medication but not information on whether prescriptions were actually filled. Information on physician-diagnosed major depression was also not available, nor was the conduct of a diagnostic interview feasible in our study. The HADS-D scale is an assessment instrument incorporating the potential flaws of self-report measurement. Thus, social desirability cannot be excluded,

and altered response behaviour due to the presence of depressive symptoms could be an issue. Furthermore, it has been argued that the HADS' latent structure may be unclear and that its depression scale may not cover all relevant symptoms of depression (the main criticism being that it ignores somatic symptoms) (Cosco et al., 2012). However, it is still commonly used and may be useful and relevant as a screening tool.

Third, some of the patients with heightened HADS scores could have received pharmacological treatment for depression. It would have been interesting to differentiate between untreated and treated depression.

Finally, patients were recruited only at one clinic specialized in the treatment of people with RA. As non-adherence may be a particular problem in patients who do not receive optimal treatment, these results cannot be transferred to RA patients in general. However, even if the sampling procedure was not designed to yield a representative sample of patients with RA, the characteristics of our sample regarding the distribution of sex, age and social status corresponded to the sample characteristics of a population-based representative study conducted in Germany (Fuchs et al., 2013). With about one-third of RA patients having HADS-D scores above the cut-off value, this proportion was also in line with data from other studies which likewise applied the HADS-D scale and the same cut-off value (Covic et al., 2012; Matcham et al., 2013).

Conclusion

This study was the first to explore the role of depression in the relationship between beliefs about medicines and medication adherence in patients with RA. The finding of a differential effect of depression is highly relevant as it informs projects which develop interventions to alter beliefs about medicines and as depression is a common comorbidity not only in RA but also in many other chronic conditions. Further research, preferably using longitudinal designs with data on the course of depression, is necessary to confirm our finding on the role of depression and to investigate whether incidence and remission of depressive episodes have an impact on the associations postulated in the 'necessity–concerns framework'.

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