Received: 23 January 2020 | Revised: 12 March 2020 | Accepted: 6 April 2020

DOI: 10.1111/hae.14011

Haemophilia WILEY

ORIGINAL ARTICLE

Clinical haemophilia

Depressive symptoms and adherence to prophylaxis in patients with haemophilia from Croatia and Slovenia

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Introduction: Adherence to a prophylactic therapy is obligatory to prevent bleeding in patients with haemophilia. It has already been recognized that depression is associated with treatment adherence.

Aim: The aim of this study was to examine the prevalence of depressive symptoms in adults with haemophilia using an instrument designed or validated for diagnosing or screening for depression and to investigate the association of symptoms of depression with nonadherence to prophylactic therapy in patients from two East European countries.

Methods: Adult patients with severe or moderate haemophilia receiving prophylaxis were eligible for the study. Depressive symptoms were assessed with BDI-II, adherence with VERITAS-Pro, demographic and socioeconomic data were collected using a questionnaire, and clinical data were obtained from medical records.

Results: Final sample included 81 participants (median age was 45 years, range 18-73 years). There were 9 (11%) participants with scores on BDI-II above 14 points, the cut-off score for depressive symptomatology. In general, participants were adherent. However, there were 14 (17%) participants who had scores above 57 points, the cut-off score for nonadherence. There was an association between having depressive symptoms and being nonadherent, and depressive symptoms explained additional variance in adherence after controlling for sociodemographic, psychosocial and clinical characteristics.

Conclusion: Since there is an association between depressive symptoms and nonadherence, it would be beneficial for both patients and the public health system for screening for depressive symptoms to be included as a part of the treatment protocol.

KEYWORDS

adherence, haemophilia, symptoms of depression

1 | INTRODUCTION

Haemophilia is a rare chronic disease that affects a small number of patients, but the costs of treatment are high in European countries, as shown by the CHESS study.[1] The vast majority of the cost burden (up to 99%) was the cost of the factor replacement therapy.[1] Nonadherence to medication regimens is a real public health problem.[2] Therefore, it is of great importance to examine and understand the factors contributing to adherence rate to prophylaxis in haemophilia. Prophylaxis diminishes frequency of bleeding; therefore, it may slow progression of joint disease and improve quality of life.[3] Patients with haemophilia (PWH)

who started prophylaxis at an early age report almost as high health-related quality of life (HRQL) as the general population.[4] Adherence to a prophylactic treatment regimen is obligatory to prevent bleeding in PWH. Although there is a huge advancement in haemophilia treatment, health outcomes will not improve if patients do not take prophylactic therapy regularly. Reported levels of adherence to prophylaxis in haemophilia have been found to vary from 44% to 87% in USA, Canada, Australia and Western European countries.[5-10] As far as we know, there are no available data for the adherence level in Eastern European countries.

It has already been recognized that depression is associated with treatment nonadherence. A meta-analysis by Grenard et al showed that depression is associated with poor adherence in many chronic diseases.[11] Recent studies corroborated this finding in patients with systematic lupus erythematosus, heart failure, hypogonadothropic hypogonadism, tuberculosis, cystic fibrosis, epilepsy and in haemodialysis patients and patients with HIV receiving antiretroviral therapy (ART).[12-21] Depression has been indicated as an important factor for nonadherence in haemophilia as well.[9,22] One of the important issues in understanding the association between depression and treatment adherence is the way depression is measured. Most of the studies that investigated depression in PWH used quality of life instruments which are not designed or validated for diagnosing or screening for depression.[22] If instruments designed for screening for depression were used, they were short instruments such as PROMIS-Depression which has 4 items or PHQ-9 which has 9 items. None of the studies used BDI-II, an instrument for indicating the presence and degree of depressive symptoms.[23]

Prevalence of depression in adults with haemophilia varied largely in different populations and as studies used different measures of depression. One study in Italy using modified Beck Inventory found the lowest prevalence of 8%,[24] a study using PHQ-9 in USA found the prevalence to be 37%,[22] it was 21% for self-reported depression diagnosis in USA,[9] 27.2% with PROMIS-Depression scale in Portugal,[25] and 33% and 32% in two UK samples with the first measuring both anxiety and depression with one item[26] and the second using a nonstandardized questionnaire developed for the study.[27] Prevalence of depression in adults with haemophilia is an important question because it has been shown that people with haemophilia with higher depression symptoms were more likely to have had urgent hospital visits,[28] bleeding episodes,[9,28] affected joints and lower quality of life.[28] There is only one study that directly examined the association between depression and adherence to factor replacement therapy.[9] Tran et al collected data from 91 males (49% on prophylaxis regimen) using the Validated Haemophilia Regimen Treatment Adherence Scale-Prophylaxis and found that self-reported depression was negatively associated with adherence, controlling for chronic medication, physician trust, quality of life and time seen at Haemophilia Treatment Centre.

To the best of our knowledge, the association of symptoms of depression in PWH using an instrument designed or validated for diagnosing or screening for depression and adherence to prophylaxis has not yet been investigated. The aim of this study was to (a) examine the prevalence of depressive symptoms in adults with haemophilia and (b) investigate the association of symptoms of depression with adherence to prophylactic therapy independent of various sociodemographic, psychosocial and clinical characteristics of patients with moderate or severe haemophilia. In addition, this study investigates this association in two East European countries, which have not been examined so far.

2 | MATERIALS AND METHODS

This cross-sectional multicentre study was conducted in the National Haemophilia Centre at University Hospital Centre Zagreb, Croatia and in the National Haemophilia Centre at University Medical Centre Ljubljana, Slovenia. Eligible patients who visited the haemophilia centre and hospitalized patients were asked to participate in the study. Patients signed informed consent forms before completing the questionnaire. The study was approved by the Ethics Committee of the University Hospital Centre Zagreb and National Medical Ethics Committee of the Republic of Slovenia. The study was conducted in accordance with the Declaration of Helsinki.

2.1 | Study population

Male patients aged 18 or older with severe or moderate haemophilia A or B who were currently using prophylactic treatment for at least one year before the recruitment were eligible for the study. Noninclusion criteria were the presence of inhibitors and cognitive impairment. One participant was excluded for taking antidepressants during the previous three months. Final sample included 81 male participants, 46 from Croatia and 35 from Slovenia. Median age of participants was 45 years (range 18-73 years). Table 1 shows demographic characteristics for the entire sample.

2.2 | Instruments

Demographic and socioeconomic data were collected using a questionnaire with information about age, education level (finished primary, secondary or tertiary education), partner status (0 = not in a relationship, 1 = in a relationship), household status (0 = living alone, 1 = living with other people), work status (0 = working age, 1 = retired), monthly household income, body mass index (BMI), smoking (not at all, sometimes, every day) and alcohol consumption (1 = never to 9 = every day).

Clinical data were obtained from the medical records and included type and severity of haemophilia, bleeding episodes during previous 12 months (1 = 11 or less, 2 = 12 or more), and hospitalizations in the previous 6 months (0 = none to 5 = longer than a month).

TABLE 1 Sample characteristics

Characteristic	Total sample N = 81	Croatian sample n = 46	Slovenian sample n = 35
Age (y)			
Median	45	37.50	47
Range	18-73	18-72	18-73
Gender, n (%)			
Male	81 (100%)	46 (100%)	35 (100%)
Diagnosis, n (%)			
Haemophilia A	70 (86%)	36 (78%)	34 (97%)
Haemophilia B	11 (14%)	10 (22%)	1 (3%)
Severity, n (%)			
Severe	76 (94%)	41 (89%)	35 (100%)
Moderate	5 (6%)	5 (11%)	0 (0%)
Education, n (%)			
Primary	9 (11%)	5 (11%)	4 (11%)
Secondary	47 (58%)	29 (63%)	18 (52%)
Tertiary	25 (31%)	12 (26%)	13 (37%)
Partner n (%)			
No	36 (44%)	17 (37%)	19 (54%)
Yes	45 (56%)	29 (63%)	16 (46%)
Household, n (%)			
Alone	15 (19%)	8 (17%)	7 (20%)
With someone	66 (81%)	38 (83%)	28 (80%)
Work status, n (%)			
Working age	53 (65%)	31 (67%)	22 (63%)
Retired	28 (35%)	15 (33%)	13 (37%)

TABLE 2 Descriptive statistics for BDI-2 and VERITAS-Pro (N = 81)

	M	Range	SD	α
VERITAS-Pro				
Total	42.14	24-72	14.07	.89
Time	6.67	4-14	2.67	.82
Dose	6.21	4-13	2.80	.65
Plan	6.09	4-12	2.27	.33
Remember	6.89	4-16	3.56	.81
Skip	7.21	4-20	4.13	.92
Communicate	9.07	4-20	4.32	.72
BDI-2				
Total	5.25	0-29	6.02	.89

2.3 | VERITAS-Pro

The Validated Haemophilia Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-Pro) was used for assessing adherence to prophylactic treatment.[29] It was developed and validated by the Indiana Haemophilia & Thrombosis Center and was provided for use. VERITAS-Pro in Croatian was provided and we translated VERITAS-Pro to Slovenian. The translation was carried out according to the international guidelines implementing forward and back translation of the instrument.[30] VERITAS-Pro is a self-reported instrument that contains six different subscales (time, dose, plan, remember, skip and communicate) and each subscale has four items.[29] Each item is rated on a five-point scale ranging from 'Always' to 'Never'.[29] Total scores range from 20 points to 120 points, higher scores indicate poorer adherence and cut-off for nonadherence is 57 points.[29] Cronbach's alpha reliabilities in this study were satisfactory for all except Plan subscale (see Table 2). One of the four items was not correlated with Total score and two other items, and if deleted Cronbach's alpha increased. However, this subscale had the lowest internal consistency and test-retest reliabilities for self-report data in the original study as well.[29]

2.4 | Beck Depression Inventory II

Beck Depression Inventory II (BDI-II) is an instrument for indicating the presence and degree of depressive symptoms consistent with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[23] It is a self-reported instrument with 21 items

TABLE 3 Intercorrelations with adherence

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)
(1) Total																		
(2) Time	**.62**																	
(3) Dose	**.74**	**.33**																
(4) Plan	**.54**	**.24**	**.23**															
(5) Remember	**.87**	**.37**	**.65**	**.54**														
(6) Skip	**.86**	**.37**	**.71**	**.43**	**.87**													
(7) Communicate	**.57**	**.41**	**.23**	.09	**.26**	.20												
(8) Depression	.19	.10	.16	.12	.16	**.24**	.04											
(9) Age	**−.23**	−.17	−.07	**−.35**	−.17	−.06	**−.23**	.12										
(10) Education	.17	.12	.11	.04	**.24**	.02	.18	−.10	−.06									
(11) Income	−.03	.08	−.05	−.05	.05	−.08	−.07	**−.41**	−.07	**.40**								
(12) Work	**−.25**	−.20	−.12	**−.24**	**−.22**	−.02	**−.29**	**.33**	**.71**	**−.32**	**−.23**							
(13) Partner	.19	.19	.17	.07	.18	.20	.00	−.04	.18	.21	**.24**	.13						
(14) Household	.01	.05	.01	.13	.08	.14	**−.27**	.01	**−.24**	.05	**.43**	−.05	**.34**					
(15) BMI	−.04	−.01	.07	−.10	.05	.01	−.17	−.01	**.26**	−.12	−.01	**.22**	.08	−.04				
(16) Smoking	.19	.10	.06	**.30**	.11	.08	.20	.04	**−.22**	**−.25**	**−.38**	−.05	−.16	−.12	−.14			
(17) Alcohol	.17	.17	.17	−.06	.10	.16	.13	−.04	.03	.05	.09	−.02	.04	.05	−.16	−.16		
(18) Bleeding	**.28**	.18	**.25**	.01	.16	**.27**	**.24**	.18	.11	−.02	−.09	.12	.01	−.05	−.11	.08	.13	
(19) Hospitalization	.07	−.03	.13	.06	.09	**.25**	−.17	**.34**	.01	−.18	**−.35**	.20	.05	−.11	−.06	−.04	−.07	**.22**

Note: All correlations in bold are significant at $P < .05$.

evaluating 21 symptoms of depression. Each item is rated on a four-point scale, total score ranging from 0 to 63 and higher scores mean higher severity of symptoms. BDI-II in Croatian was provided by Naklada Slap and BDI-II in Slovenian was provided by NCS Pearson, Inc, copyright holders for Croatian and Slovenian, respectively. Cronbach's alpha reliability in this study was .89.

2.5 | Statistical analysis

All statistical analyses were run in SPSS 26.0.[31] We first examined descriptive statistics, including frequencies, means, medians, standard deviations, normality of distributions (Kolmogorov-Smirnov and Shapiro-Wilk tests) and reliabilities. Next, we ran correlational and regression analyses. Statistical significance was set at $P < .05$.

3 | RESULTS

Descriptive statistics for BDI-II and VERITAS-Pro are shown in Table 2. Tests of normality indicated that our data were not normally distributed. We then examined the values of skewness and kurtosis coefficients, and they were in the range of the suggested values for the distribution to be considered approximately normal,[32] except for Skip subscale and BDI-II total score.

Our first aim was to examine the prevalence of depressive symptoms in adults with haemophilia receiving prophylactic therapy. Participants in our study had, in general, low levels of depressive symptoms as indicated by their mean score on BDI-II (M = 5.25, SD = 6.02). However, there were 9 (11%) participants with scores above 14 points, the cut-off score for depressive symptomatology. In other words, prevalence of depressive symptoms in adults with haemophilia receiving prophylaxis in samples from Croatia and Slovenia using BDI-II was 11%. Higher scores on BDI-II were significantly associated with lower monthly income, being retired and longer hospitalization during the last 6 months.

Next, we examined the level of adherence in our sample. In general, participants in our study were adherent, as indicated by the mean score on VERITAS-Pro (M = 42.14, SD = 14.07). However, there were 14 (17%) participants who had scores above 57 points, the cut-off score for nonadherence.

In order to get answers for our second aim, we first ran correlational analysis. Correlations between sociodemographic, psychosocial and clinical characteristics of patients and their depressive symptoms with adherence are shown in Table 3. Three sociodemographic variables had significant correlations, age with Total score, Plan and Communicate subscales, work with Total score, Plan, Remember and Communicate subscales, and education with Remember subscale. We found only one significant correlation for a psychosocial variable, having a partner, and Communicate subscale. Out of clinical characteristics, smoking was correlated with Plan subscale, bleeding episodes with Total score, Dose, Skip and Communicate subscales, and hospitalizations with Skip subscale. Taken together, these findings indicate that those who were more adherent were older, retired, less educated, living with someone, nonsmoking, had 11 or less bleeding episodes in the last year and fewer hospitalizations.

Finally, depressive symptoms were not significantly correlated with Total score, but were with Skip subscale, indicating that better adherence was associated with having less depressive symptoms. Since both BDI-II and Skip subscale scores were not normally distributed, we also calculated Spearman's correlation which indicated the same ($r_s = .29$, $P = .009$). To further examine the association between depressive symptoms and adherence, we categorized VERITAS-Pro and BDI-II total scores into below and above the cut-off scores categories. We then tested whether there was a significant difference between the expected and the observed frequencies in those categories, and found a significant difference ($\chi^2(1, N = 81) = 5.22$, $P = .022$, $V = 0.25$). In other words, there was an association between having depressive symptoms and being nonadherent. However, based on the size of Cramer's V index, it was a weak association.

We then ran regression analysis with all our variables, except alcohol consumption since it showed no significant correlations with any of our variables. All variables, except BDI-II, were entered in the first step, and BDI-II was entered in the second step. In the first step, 17.5% of adherence variance was explained ($F(10, 69) = 2.67$, $P = .008$) with partner ($\beta = .26$, $P = .03$) and bleeding episodes ($\beta = .30$, $P = .007$) as significant predictors. Depressive symptoms explained additional 5.9% of adherence variance ($F(11, 68) = 3.16$, $P = .002$; $\Delta F(1, 68) = 6.11$, $P = .016$). Significant predictors were partner ($\beta = .29$, $P = .014$), bleeding episodes ($\beta = .27$, $P = .011$) and depressive symptoms ($\beta = .30$, $P = .016$). The full model explained 23.2% of adherence variance and showed that in our sample not being in a relationship, having 11 or less bleeding episodes in the last year and having fewer depressive symptoms predicted adherence to prophylaxis.

4 | DISCUSSION

This study investigated the association of symptoms of depression in PWH using an instrument designed or validated for diagnosing or screening for depression and adherence to prophylaxis in two East European countries which have not been examined so far. We first examined the prevalence of depressive symptoms in adults with haemophilia. We found using BDI-II that the prevalence of depressive symptoms in adults with haemophilia receiving prophylaxis in samples from Croatia and Slovenia was 11%. This finding is not in line with most studies examining the prevalence of depression in adults with haemophilia, which found higher prevalence in the 21%-37% range.[9,22,25-27] However, none of these studies used an instrument designed or validated for diagnosing or screening for depression. One study, using a modified Beck Inventory, found the prevalence of 8%,[24] which is similar to our finding. It seems that the prevalence of depressive symptoms in PWH is around 10% when

an instrument designed or validated for diagnosing or screening for depression is used.

Level of adherence to prophylaxis in haemophilia has also not been examined so far in Eastern European countries. Data for the adherence level from USA, Canada, Australia and Western European countries have been found to vary from 44% to 87%.[5-10] Our data indicated that 83% of the sample was adherent. In line with previous findings that depression is an important factor for adherence in many chronic diseases including haemophilia,[9,11-22] our correlational and regression analyses, as well as chi-square test, indicated that those having depressive symptoms are at more risk of being nonadherent to prophylaxis. Depressive symptoms explained additional variance in adherence after controlling for sociodemographic, psychosocial and clinical characteristics of patients associated with adherence. This has an important implication for PWH receiving prophylactic therapy. Perhaps screening for depressive symptoms should be included as part of the treatment protocol, in order to minimize both personal and medical costs of nonadherence of patients with depressive symptoms.

This study also has some limitations. Due to the cross-sectional nature of the study, a causal inference cannot be made. Bleeding episodes showed significant association with adherence in both correlational and regression analyses but were only measured as a dichotomized variable. Future studies should further explore this association. Reliability of Plan subscale was low in both subsamples, but lower in Croatian so this should be checked in future studies. This could be due to the dispensation schedule and protocol in Croatia and Slovenia. In Croatia, patients have their prophylaxis prescription refilled once a year, and in Slovenia, every 3 months.

5 | CONCLUSION

The prevalence of depressive symptoms in PWH receiving prophylaxis in samples from Croatia and Slovenia, using an instrument designed and validated for diagnosing or screening for depression, was 11%. Adherence level in our sample was 83%. Depressive symptoms explained additional variance in adherence after controlling for sociodemographic, psychosocial and clinical characteristics of patients. Variables not being in a relationship, having 11 or less bleeding episodes in the last year and having fewer depressive symptoms predicted 23.2% of adherence to prophylaxis variance. Since there is an association between depressive symptoms and nonadherence, it would be beneficial for both patients and the public health system for screening for depressive symptoms to be included as a part of the treatment protocol.

ACKNOWLEDGEMENTS

MB designed the study; MB, IPZ, BFK and SZS collected data; AB analysed data, MB, AB, IPZ, BFK, IP, VBV and SZS wrote the manuscript, VBV and SZS revised the manuscript. The authors have no competing interests.

DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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How to cite this article: Bago M, Butkovic A, Preloznik Zupan I, et al. Depressive symptoms and adherence to prophylaxis in patients with haemophilia from Croatia and Slovenia. *Haemophilia*. 2020;26:e161–e167. https://doi.org/10.1111/hae.14011