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Lower Adherence to Clotting Factor Replacement Therapy in Patients with Haemophilia Associated with More Depressive Symptoms: Two Centers Cross-Sectional Study

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The aim of this study was to examine the association of depressive symptoms with medication adherence levels in a combined sample from Croatia and Slovenia. Participants in the study were adult patients with haemophilia receiving prophylaxis or on-demand treatment (N = 109). Their age was between 18 and 73 years (M = 43.86, SD = 14.89). Self-reported medication adherence (implementation phase) was measured with The Validated Haemophilia Regimen Treatment Adherence Scale, while depressive symptoms were measured with Beck Depression Inventory II. Comparison of adherence scores using t-test indicated that participants using prophylaxis were more adherent than participants using on-demand treatment on total scale and time and plan subscales. In hierarchical regression analyses depressive symptoms were a significant predictor for the total score and time subscale after controlling for sociodemographic and clinical variables. Screening for depressive symptoms and improving medication adherence of patients using on-demand treatment is recommended.

Key words: medication adherence, depressive symptoms, patients with haemophilia

Introduction

Haemophilia is a rare condition that impairs the ability of the body to make blood clots and stop bleedings. In order to avoid longer bleedings or bleedings into joints patients with haemophilia (PWH) need to take clotting factor replacement therapy either regularly (prophylaxis) or on-demand (Srivastava et al.,

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2013). Adherence to clotting factor replacement therapy in haemophilia is obligatory to prevent bleedings. In addition, haemophilia treatment has prolonged the average life expectancy for PWH to a near-normal life expectancy (Darby et al., 2007). But haemophilia treatment has high costs both for the patients and healthcare systems with the highest costs being clotting factors (O'Hara et al., 2017). Therefore, it is of great importance to understand how and why PWH become non-adherent to their medication. Reported levels of medication adherence to prophylaxis and on-demand treatment in PWH have been found to vary from 44% to 87% (De Moerloose et al., 2008; du Treil et al., 2007; Ho et al., 2014; Krishnan et al., 2015; Lamiani et al., 2015; Llewellyn et al., 2003; Torres-Ortuño et al., 2018; Tran et al., 2017; Zappa et al., 2012).

It has been shown in many chronic diseases that one of the factors associated with medication adherence are depressive symptoms. A meta-analysis on depression and medication adherence in chronic diseases (Grenard et al., 2011) analyzed 31 studies with 18,245 participants covering different diseases such as coronary heart disease, diabetes, hypertension, and asthma. Results showed that depressed patients had 1.76 times the odds of being non-adherent compared to patients who were not depressed, and that method of adherence measurement was a significant moderator. Further studies on patients with systemic lupus erythematosus (Abdul-Sattar & Abou El Magd, 2015; Alsowaida et al., 2018), heart failure (Gathright et al., 2017), hypogonadothropic hypogonadism (Dwyer et al., 2017), tuberculosis (Yan et al., 2018), cystic fibrosis (Hilliard et al., 2015), epilepsy (Ettinger et al., 2014; Guo et al., 2015), in haemodialysis patients (Ossareh et al., 2014) and patients with HIV receiving antiretroviral therapy (ART) (Belenky et al., 2014) also found that depressive symptoms and non-adherence are associated.

Few studies so far have examined the association of depression with medication adherence in a combined sample of PWH on either prophylaxis or on-demand treatment. Tran et al. (2017) examined the association with self-reported current or past diagnosis of depression and found that a history of depression was associated with lower medication adherence. Witkop et al. (2019) examined this association using The Patient Health Questionnaire 9-item depression module (PHQ-9) and also found that depression was associated with lower adherence to clotting factor treatment in adult PWH. These studies used a self-reported history of depression or a short measure, and both studies used The Validated Haemophilia Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-Pro) and The Validated Haemophilia Regimen Treatment Adherence Scale-PRN (VERITAS-PRN) self-reported measures of medication adherence.

In this study the objective was to examine the association of depressive symptoms, assessed with a widely used and accepted measure of depressive symptomatology, easy to use and with good psychometric properties (Beck et al., 1996), with medication adherence levels in a combined sample of PWH on either prophylaxis or on-demand treatment from Croatia and Slovenia. We hypothesized that depressive symptoms will be associated with lower medication adherence in PWH, after controlling for sociodemographic and clinical variables.

Method

Participants and Procedure

Participants in the study were adult patients with haemophilia receiving prophylaxis or on-demand treatment (*N* = 109). Sample

characteristics for the total sample and patients using on-demand treatment are shown in Table 1. Participants using prophylaxis are described in more detail in Bago et al. (2020). The sample in this study comprised patients (74% on prophylaxis, 77% with severe haemophilia) who regularly came to the haemophilia centre or were hospitalized in the Croatian national Haemophilia Centre at University Hospital Centre Zagreb, Croatia (*n* = 64) and in the Slovenian national Haemophilia Centre at University Medical Centre Ljubljana, Slovenia (*n* = 45), and met the eligibility criteria. Data were collected from April 2018 to October 2019. All approached patients agreed to take part in the study. Participants' age was between 18 and 73 years (*M* = 43.86, *SD* = 14.89). Both facilities in which patients were recruited provided both types of patients (prophylaxis and on-demand treatment). The Ethics Committee of the University Hospital Centre Zagreb and the National Medical Ethics Committee of the Republic of Slovenia approved the study, which was conducted in accordance with the Declaration of Helsinki. Before completing the measures, participants signed the informed consent form.

Measures

Sociodemographic data were collected via questionnaire which included questions about age, relationship status (0 = do not have a partner, 1 = have a partner), household status (0 = living alone, 1 = living with other people), work status (0 = working age, 1 = retired), and smoking (1 = not at all, 2 = sometimes, 3 = every day). Since our participants were either outpatients at the haemophilia centre or were hospitalized there, information about their arthropathy diagnosis (0 = no, 1 = yes) was obtained from their medical records, while they were asked about bleeding episodes during the previous 12 months (1 = 11 or less, 2 = 12 or more) and hospitalizations in the previous 6 months (0 = no, 1 = yes). These questions were chosen because previous studies indicated that having more excessive bleedings (e.g., more than once a month during the last year) or being hospitalized could be associated with medication adherence levels (e.g., Pérez-Robles et al., 2016; van Os et al., 2017).

Self-reported depressive symptoms were assessed with Beck Depression Inventory II (BDI-II; Beck et al., 1996), a 21-items instrument for indicating the presence and degree of 21 depressive symptoms consistent with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Participants in Croatia filled in the validated Croatian translation (Jakšić et al., 2013) and participants in Slovenia filled in the Slovenian translation (Golja et al., 2020; Zupančič & Bitenc, 2019). Participants had to rate each item on a four-point scale with the total score ranging from 0 to 63 and higher scores indicating higher severity of symptoms. Beck et al. (1996) suggested the following cut-off scores: minimal (0–13), mild (14–19), moderate (20–28), and severe depression (29–63). Cronbach's alpha for the total score in the whole sample was .90.

Self-reported medication adherence (implementation phase) was measured with The Validated Haemophilia Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-Pro; Duncan et al., 2010a) for participants using prophylactic treatment and The Validated Haemophilia Regimen Treatment Adherence Scale-PRN (VERITAS-PRN; Duncan et al., 2010b) for participants using on-demand treatment. Both VERITAS scales have a total of 24 items divided into six different subscales with each subscale having four items. VERITAS-Pro has subscales time, dose, plan, remember, skip, and communicate while VERITAS-PRN has subscales treat, time, dose, plan, remember,

Table 1 *Sample characteristics*

Characteristic	Total sample *N* = 109	On-demand *n* = 28
Age (years)		
Median (range)	46 (18-73)	48.50 (18-69)
Mean (*SD*)	43.86 (14.89)	45.29 (15.24)
Diagnosis – *n* (%)		
Haemophilia A	93 (85%)	23 (82%)
Haemophilia B	15 (14%)	4 (14%)
Missing data	1 (1%)	1 (4%)
Severity – *n* (%)		
Severe	84 (77%)	8 (29%)
Moderate	12 (11%)	8 (29%)
Mild	11 (10%)	11 (39%)
Missing data	2 (2%)	1 (3%)
Partner – *n* (%)		
No	44 (40%)	8 (29%)
Yes	65 (60%)	20 (71%)
Household – *n* (%)		
Alone	21 (19%)	6 (21%)
With someone	88 (81%)	22 (79%)
Work status – *n* (%)		
Working age	74 (68%)	21 (75%)
Retired	35 (32%)	7 (25%)
Arthropathy – *n* (%)		
No	32 (29%)	15 (54%)
Yes	74 (68%)	11 (39%)
Missing data	3 (3%)	2 (7%)
Bleedings – *n* (%)		
11 or less	76 (70%)	18 (64%)
12 or more	33 (30%)	10 (36%)
Hospitalizations – *n* (%)		
No	92 (84%)	21 (75%)
Yes	17 (16%)	7 (25%)

Note. Severity = Depending on the amount of the clotting factor in a person's blood haemophilia can be mild (>5% to <40% factor activity), moderate (1% to 5% factor activity), or severe (<1% factor activity).

and communicate. Items in time subscales measure infusing the clotting factor at the right time, in dose subscales using the recommended dose of the clotting factor, in plan subscales planning to have enough factor, in remember subscales remembering to infuse the clotting factor, in skip subscale skipping the clotting factor infusions, in treat subscale infusing the clotting factor if needed, and in communicate subscales communicating with the haemophilia treatment centre when having treatment questions. Participants had to

rate each item on a five-point scale ranging from 1 = always to 5 = never, meaning that subscale scores ranged from 4 to 20 points and a total score from 24 to 120 points, and that a higher score indicated lower medication adherence levels. Cronbach's alpha for the total score in the whole sample was .89 for VERITAS-Pro and .77 for VERITAS-PRN. For VERITAS-Pro subscales Cronbach's alpha reliabilities were in the .33-.92 range, while for VERITAS-PRN they were in the .41-.77 range. VERITAS scales have been validated for adults in the US (Duncan et al., 2010a, 2010b), Spain (Cuesta-Barriuso et al., 2017; Torres-Ortuño et al., 2021), Brazil (Ferreira et al., 2018) and Germany (von Mackensen et al., 2020).

Analytical Strategy

We first examined descriptive statistics, including frequencies, means, medians, standard deviations, and reliabilities. We examined mean differences in adherence scores between two types of treatment with *t*-test for independent samples. Next, we ran correlational and regression analyses.

Results

Descriptive statistics for medication adherence scores are presented in Table 2. Participants on prophylaxis had a total adherence score in the 24-72 points range (*M* = 42.14, *SD* = 14.07), while participants using on-demand treatment had a total adherence score in the 33-80 points range (*M* = 52.18, *SD* = 13.11). The highest subscale scores for participants on prophylaxis were found on communicate (*M* = 9.07, *SD* = 4.32, range: 4-20) and skip (*M* = 7.21, *SD* = 4.13, range: 4-20) subscales, while for participants using on-demand treatment the highest subscale scores were found on communicate (*M* = 11.07, *SD* = 4.86, range: 4-20) and time (*M* = 10.79, *SD* = 3.98, range: 4-18) subscales. Comparison of medication adherence scores using *t*-test indicated that participants using on-demand treatment had higher total adherence score and higher time and plan subscale scores than participants using prophylaxis, after Bonferroni correction of *p* value due to multiple comparisons ($p < .007$). As could be expected,

Table 2 *Descriptive statistics for medication adherence scores and comparison between PWH using prophylaxis and PWH using on-demand treatment*

	VERITAS-Pro (*n* = 81)	VERITAS-PRN (*n* = 28)		
VERITAS-Pro/PRN	*M* (*SD*)	*M* (*SD*)	*t* (*p*)	*d*
Total	42.14 (14.07)	52.18 (13.11)	3.31 (.001)	-0.52
Time	6.67 (2.67)	10.79 (3.98)	6.15 (<.001)	-1.22
Dose	6.21 (2.80)	7.89 (3.26)	2.62 (.01)	-0.55
Plan	6.09 (2.27)	8.43 (4.48)	3.57 (<.001)	-0.66
Remember	6.89 (3.56)	6.18 (3.22)	0.93 (.353)	0.21
Skip/Treat	7.21 (4.13)	7.82 (3.39)	0.70 (.483)	-0.16
Communicate	9.07 (4.32)	11.07 (4.86)	2.04 (.043)	-0.43

Note. VERITAS-Pro = The Validated Haemophilia Regimen Treatment Adherence Scale-Prophylaxis; VERITAS-PRN = The Validated Haemophilia Regimen Treatment Adherence Scale-PRN; *M* = arithmetic mean; *SD* = standard deviation; *t* = *t* – test; *p* = *p* – value; *d* = Cohen's *d*

participants on prophylaxis report, on average, better medication adherence levels than participants using on-demand treatment. Effect sizes measured with Cohen's *d* were small for the total score, moderate for plan subscale and large for time subscale. We also tested for difference in depression severity between these two groups. Given the violations of Levene's test for homogeneity of variances (F = 12.46, p = .001), t-test not assuming homogeneous variances was run and showed no difference between the groups (t (36.42) = -1.34, p = .190).

Further, we examined bivariate associations between medication adherence levels and sociodemographic and clinical variables, and depressive symptoms. These associations are presented in Table 3. Total adherence score was negatively associated with age (r = -.20, p = .036), being retired (r = -.22, p = .020) and arthropathy (r = -.25, p = .011) and positively associated with depressive symptoms (r = .20, p = .041). Communicate subscale was negatively associated with age (r = -.26, p = .006), living with someone (r = -.24, p = .014), being retired (r = -.24, p = .013) and positively with having 12 or more bleeding episodes during the previous 12 months (r = .22, p = .024). Time subscale was positively associated with having a partner (r = .22, p = .023) and depressive symptoms (r = .26, p = .006) while it was negatively associated with arthropathy (r = -.25, p = .009). Plan subscale was positively associated with smoking (r = .31 p = .001) and negatively with arthropathy (r = -.25, p = .009), which was also negatively associated with dose subscale (r = -.21, p = .029). Remember subscale was only negatively associated with age (r = -.24, p = .012), while skip/treat subscale was not significantly associated with any of the variables.

Next, we ran a series of hierarchical regression analyses predicting each adherence score with sociodemographic variables entered in the first step, clinical variables entered in the second step and depressive symptoms entered in the third step. Regression coefficients from the third step are presented in Table 4. In line with correlational results, full regression models were not significant for dose, remember and skip/treat subscales. Depressive symptoms were a significant predictor for the total score and time subscale. For the total score, partner (β = .28, p = .009), bleedings (β = .19, p = .049), and depressive symptoms (β = .23, p = .018) were significant predictors

Table 3 *Bivariate associations between medication adherence levels and sociodemographic and clinical variables, and depressive symptoms*

	VERITAS-Pro/PRN						
	Total	Time	Dose	Plan	Remember	Skip/treat	Communicate
Age	-0.20*	-0.06	-0.07	-0.14	-0.24*	-0.01	-0.26**
Partner	0.16	0.22*	0.12	0.15	0.05	0.18	-0.05
Household	0.03	0.07	-0.02	0.17	0.09	0.12	-0.24*
Work	-0.22*	-0.17	-0.15	-0.14	-0.18	-0.01	-0.24*
Smoking	0.19*	0.11	0.04	0.31**	0.06	0.08	0.16
Arthropathy	-0.25*	-0.25**	-0.21*	-0.25**	-0.07	-0.10	-0.15
Bleedings	0.17	0.05	0.16	-0.04	0.07	0.19	0.22*
Hospitalization	0.07	0.11	0.04	0.12	0.02	0.11	-0.07
BDI-II	0.20*	0.26**	0.08	0.11	0.10	0.18	0.06

Note. VERITAS-Pro = The Validated Haemophilia Regimen Treatment Adherence Scale-Prophylaxis; VERITAS-PRN = The Validated Haemophilia Regimen Treatment Adherence Scale-PRN; BDI-II = Beck Depression Inventory II.

* p < 0.05; ** p < 0.01

Table 4 *Results of the regression analyses for medication adherence scores*

	Total	Time	Dose	Plan	Remember	Skip/treat	Communicate
Step 1	F1 (6, 99) = 4.04*, Adj. R^2 = .15	F1 (6, 99) = 6.56*, Adj. R^2 = .24	F1 (6, 99) = 1.81, Adj. R^2 = .04	F1 (6, 99) = 6.40*, Adj. R^2 = .24	F1 (6, 99) = 1.26, Adj. R^2 = .02	F1 (6, 99) = 0.92, Adj. R^2 = .00	F1 (6, 99) = 4.10*, Adj. R^2 = .15
Age	β = -.18	β = -.05	β = .00	β = -.05	β = -.22	β = -.01	β = -.33*
Partner	β = .28*	β = .21*	β = .21	β = .11	β = .17	β = .21	β = .22*
Household	β = -.10	β = -.02	β = -.12	β = .14	β = -.01	β = .05	β = -.37*
Work	β = -.14	β = -.21	β = -.11	β = -.11	β = -.11	β = -.05	β = -.02
Smoking	β = .12	β = .09	β = -.02	β = .30*	β = .01	β = .05	β = .06
Treatment group	β = -.18	β = -.38*	β = -.13	β = -.29*	β = .13	β = .02	β = -.12
Step 2	F2 (9, 96) = 3.61*, Adj. R^2 = .18	F2 (9, 96) = 4.33*, Adj. R^2 = .22	F2 (9, 96) = 2.08*, Adj. R^2 = .09	F2 (9, 96) = 4.24*, Adj. R^2 = .22	F2 (9, 96) = 1.08, Adj. R^2 = .01	F2 (9, 96) = 1.41, Adj. R^2 = .03	F2 (9, 96) = 4.00*, Adj. R^2 = .21
Arthropathy	β = -.13	β = -.04	β = -.20	β = -.05	β = -.02	β = -.13	β = -.11
Bleedings	β = .19*	β = -.02	β = .21*	β = -.05	β = .11	β = .21	β = .23*
Hospitalization	β = -.06	β = -.04	β = -.01	β = .03	β = -.04	β = .03	β = -.16
Step 3	F3 (10, 95) = 3.99*, Adj. R^2 = .22	F3 (10, 95) = 5.15*, Adj. R^2 = .28	F3 (10, 95) = 1.91, Adj. R^2 = .08	F3 (10, 95) = 3.92*, Adj. R^2 = .22	F3 (10, 95) = 1.33, Adj. R^2 = .03	F3 (10, 95) = 1.48, Adj. R^2 = .04	F3 (10, 95) = 3.82*, Adj. R^2 = .21
BDI-II	β = .23*	β = .28*	β = .07	β = .10	β = .20	β = .15	β = .14

Note. Treatment group: 0 = on-demand, 1 = prophylaxis; BDI-II = Beck Depression Inventory II; *F* = *F* – ratio; Adj. R^2 = adjusted coefficient of multiple determination; β = standardized regression coefficient.

* $p < 0.05$

explaining 22% of the variance. For time subscale significant predictors were partner (β = .21, p = .040), treatment group (β = -.38, p < .001) and depressive symptoms (β = .28, p = .003) explaining 28% of the variance. For plan subscale 22% of the variance was explained with smoking (β = .31, p = .001) and treatment group (β = -.29, p = .004) as significant predictors. For communicate subscale 21% of the variance was explained with age (β = -.33, p = .010), partner (β = .22, p = .045), household (β = -.37, p = .001) and bleedings (β = .23, p = .015) as significant predictors.

Discussion

Previous studies on patients suffering from different chronic diseases, including haemophilia, have shown that depressive symptoms and medication adherence are associated (e.g., Grenard et al., 2011; Tran et al., 2017; Witkop et al., 2019). However, different measures of depression severity were used and BDI-II, a widely used and accepted measure of depression severity, has not been used so far in PWH. The objective of this study was to examine the association between depressive symptoms and medication adherence in the combined sample of PWH on either prophylaxis or on-demand treatment from Croatia and Slovenia. This study adds to the body of literature indicating in different populations that depressive symptoms should be checked among patients with chronic diseases. In the United States screening for depression is recommended in groups with increased risk for depression, for example persons with chronic diseases (Siu et al., 2016).

Our results indicated that PWH using prophylaxis had lower medication adherence scores than patients using on-demand treatment, indicating that they were more adherent. This finding is in line with Tran et al. (2017), who state that medication adherence was positively associated with being prescribed a prophylaxis regimen. Both groups of patients in our study had high scores or low adherence on communicate subscale indicating that in both groups low adherence is associated with problems in communication. However, the largest mean difference, as indicated by Cohen's d, was found between PWH on prophylaxis and on-demand treatment on time subscale. This means that PWH on prophylaxis pay more attention to administrating factor replacement therapy at a correct time compared to PWH using on-demand treatment.

Examining the associations of sociodemographic and clinical variables, and depressive symptoms with medication adherence confirmed the results of previous studies (Tran et al., 2017; Witkop et al., 2019) and our hypothesis. For total adherence score, depressive symptoms were a significant predictor after controlling for sociodemographic and clinical variables. In other words, higher medication adherence scores in PWH were predicted by having a partner, having more bleedings, and having more depressive symptoms. This indicates that PWH having a partner, more bleedings and more depressive symptoms report more non-adherence. Depressive symptoms were significant predictor for one subscale score, time, together with having a partner and being on on-demand treatment. As for the total score, having a partner was a significant predictor of non-adherence. Since time subscale measures if PWH administer factor replacement therapy at a correct time, this might indicate that obligations and plans in the relationship can interfere with administrating factor replacement therapy at a correct time. For other subscale scores, depressive symptoms were not a significant predictor, but regression analyses indicated that different variables are significant predictors for different aspects of medication adherence. This is important because if we want to influence the

medication adherence of PWH it is crucial to know which factors are associated with which aspects of medication adherence.

In order to tailor specific interventions to enhance medication adherence we need to examine different factors that are associated with medication adherence because it is a complex phenomenon, and also use health psychology theories. There are a number of different health behavior theories that have been used so far in studies to explain and predict medication adherence, with the most prevalent being applications of social cognitive theory, specifically the health belief model, the theory of reasoned action and the theory of planned behavior (Holmes et al., 2014). Several studies have tried to examine the association between depressive symptoms and medication adherence using health behavior theories. Manning and Bettencourt (2011) have shown that the relation between depressive symptoms and lack of medication adherence was fully mediated by the planned behavior process, while Sainsbury et al. (2013) have shown that a higher incidence of depressive symptoms had a direct negative effect on medication adherence controlling for the theory of planned behavior variables. Magidson et al. (2015) tested three components of behavioral theory and found that depressive symptoms were associated with greater nonadherence through greater environmental punishment.

As with any study, this one has specific limitations. Medication adherence was measured with a self-reported measure which is, as any self-reported measure, biased and vulnerable to socially desirable responding. It would be important to examine the association between depressive symptoms and objectively measured medication adherence since studies examining this association so far have only used self-reported measures. However, neither method can be considered a gold standard since both have advantages and disadvantages (Osterberg & Blaschke, 2005). This was a cross-sectional study and therefore we cannot conclude anything about the temporal relationship between depressive symptoms and non-adherence. The study combined PWH on prophylaxis and on-demand treatment, which might have obscured some important differences since it is possible that the subjective and objective treatment barriers to medication adherence differ in these two groups of patients.

To conclude, our results confirmed previous findings and we showed that depressive symptoms measured with BDI-II are associated with lower total adherence, after controlling for sociodemographic and clinical variables in a combined sample of PWH using either prophylaxis or on-demand treatment. In addition, we examined this association for all six subscales, and found that depressive symptoms are associated with lower adherence for time subscale as well. Since we confirmed previous findings that depressive symptoms are associated with lower medication adherence to factor replacement therapy in PWH, it is of great importance for medication adherence that PWH are screened for depressive symptoms. Medication adherence levels in patients using on-demand treatment should be improved. Future studies could further examine if health behavior theories can explain the association between depressive symptoms and medication adherence, and contribute to the understanding of the differences in adherence of PWH using prophylaxis and on-demand treatment.

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