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Predictors of non-adherence to prescribed prophylactic clotting-factor treatment regimens among adolescent and young adults with a bleeding disorder

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Introduction: Adherence to clotting-factor treatment regimens, especially among adolescents and young adults (AYAs), is under-researched. **Aim:** We determined factors associated with better adherence to prophylaxis. **Methods:** From April through December 2012, a convenience sample of AYA (aged 13–25 years) persons with haemophilia or von Willebrand disease (VWD) completed an online survey that assessed adherence to prescribed prophylactic treatment regimens [Validated Haemophilia Regimen Treatment Adherence Scale (VERITAS)-Pro]. Logistic regression analysis assessed demographic and clinical factors related to non-adherence (VERITAS-Pro≥57). **Results:** Seventy-three prophylactically treating AYAs participated. Of which, 88%, 8% and 4% had haemophilia A, B and VWD respectively. Almost all (90%) had severe disease and 58% had never developed an inhibitor. Most were aged 13–17 years (56%), white (78%), non-Hispanic (88%), never married (94%) and had some type of health insurance (96%). Median VERITAS-Pro score was 48 (range = 25–78) and 22 (30%) participants were non-adherent to prophylaxis (VERITAS-Pro≥57). Final logistic regression modelling suggested that, compared to those aged 13–17 years, participants aged 18–25 years were 6.2 (95% CI: 1.8–21.0; $P < 0.01$) times more likely to be non-adherent. Compared to respondents whose mother had at least a Bachelor's degree, respondents whose mother did not were 3.8 (95% CI: 1.0–14.3; $P = 0.05$) times more likely to be non-adherent. **Conclusions:** Results suggest that adherence efforts should be especially targeted to young adults as they transition from adolescence (i.e. parental supervision) and assume primary responsibility for their bleeding disorder care. Healthcare providers should be mindful of AYAs whose mothers have less formal education and ensure that adequate time and resources are dedicated to family adherence education.

Keywords: adherence, adolescents, predictors, prophylaxis/prophylactic, young adult

Introduction

Research over the past 50 years has demonstrated that using prophylactic treatment regimens in children with haemophilia can prevent repeated bleeding into the joints, subsequently reducing hospitalization, chronic pain, and disability – ultimately resulting in improved quality of life (QoL) [1–4]. Prophylaxis in children with severe haemophilia is a *grade 1A* recommendation based on strong evidence from both randomized controlled trials and observational research [5]. There is less consensus, however, about whether prophylaxis is ideal for adolescent and adult persons with haemophilia (PWH) [6–8]. The clinical advantages of continuing prophylaxis into adulthood have to be weighed against more pragmatic considerations like more frequent infusions and greater medical expense [7]. There is, however, a growing body of evidence suggesting that continuing prophylaxis, or starting secondary prophylaxis, in adolescents and young adult (AYA) PWH reduces the risk of bleeding and helps decrease chronic pain and preserve joint health and QoL [3,8–11].

Despite evidence demonstrating the benefits of prophylaxis, most data suggest that <50% of patients actually follow their prescribed treatment regimens in

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the United States [12–15]. Many factors are thought to influence haemophilia treatment adherence, including knowledge about the disease and the importance of treatment, disease severity and the frequency of haemophilia symptoms, treatment satisfaction, frequency of administration, the amount of time spent in an haemophilia treatment centre (HTC), reminder telephone calls, the age of the PWH, and the quality of relationships among patients and their healthcare professionals [13,16–20]. Previous studies, however, have not used standardized definitions of adherence, which makes contextualizing and comparing results difficult [12,13,17,21], and adherence among AYA PWH remains particularly under-researched. Exploring adherence among AYA PWH may be especially important given that adolescence and young adulthood represents an inflexion point, where PWH start to take more responsibility for the management of their own disease and develop treatment habits that can carry-over into adult life [13]. This survey determined factors associated with better adherence to prescribed prophylactic regimens among AYAs with a bleeding disorder using a standardized and validated tool.

Materials and methods

Study population and recruitment

Data describing AYA PWH's adherence to prescribed treatment regimens and level of chronic pain were obtained as part of the larger Interrelationship between Management of Pain, Adherence to Clotting-factor Treatment, and Quality of Life (IMPACT QoL) study, which has been previously described [3]. Data were collected via a one-time, cross-sectional, online survey from a convenience sample of AYA patients with a bleeding disorder. To be eligible to complete the survey, participants had to (i) be aged 13–25 years, (ii) read, write and speak English, and (iii) have haemophilia A, haemophilia B or von Willebrand disease (VWD). Recruitment occurred at major US haemophilia meetings (e.g. Inhibitor Summits and national and state haemophilia society meetings), HTC and through a Facebook™ (Facebook, Menlo Park, CA, USA) page dedicated to the study from April through December of 2012. All surveys were completed electronically using SurveyMonkey™ (SurveyMonkey, Palo Alto, CA, USA) and Apple iPads™ (Apple, Cupertino, CA, USA). The study was approved by the Munson Medical Center (Traverse City, MI, USA) institutional review board prior to data collection. All data were de-identified prior to analysis [3].

This study uses a patient subset of the IMPACT QoL survey data to determine factors associated with better adherence to prophylactic clotting-factor treatment regimens among AYA (aged 13–25 years) PWH or VWD. Patients who treated with on-demand regimens were excluded from this analysis because of small sample size and to minimize heterogeneity in the assessment of the primary hypothesis. Furthermore, unlike the Validated Haemophilia Regimen Treatment Adherence Scale (VERITAS)-Pro for prophylactic patients, a validated cut-off of adherence vs. non-adherence using the VERITAS-PRN for on-demand patients has not been established [22].

Measurement

Prophylactic adherence was assessed using the VERITAS-Pro [23]. Possible subscale scores range from four points (most adherent) to 20 (least adherent), and possible total scores ranged from 24 (most adherent) to 120 (least adherent) [23]. Scores were calculated for the overall VERITAS-Pro and for each of the six VERITAS-Pro subscales (Time, Dose, Plan, Remember, Skip and Communicate) which are designed to capture the diverse dimensions of adherence [23]. The cut-off for non-adherent prophylactic patients was a total VERITAS-Pro score $\geq$57 as established previously [23]. VERITAS-Pro scores were self-reported. Other self-reported data collected including information about participant age, gender, race, ethnicity, health insurance status/type and the educational level of the participants' parents. Data were also collected about bleeding disorder type (haemophilia A or B, or VWD), whether or not the participant ever developed an inhibitor to treatment, and bleeding disorder severity. For haemophilia A and B, severity was classified as mild, moderate, or severe corresponding to 6–50%, 1–5% and <1%, respectively, of the normal amount of clotting factor VIII/IX. VWD was classified as mild, moderate or severe corresponding to type I (lower than normal levels of von Willebrand factor), type II (lower than normal levels and improper functioning of von Willebrand factor) and type III disease (absence of von Willebrand factor in the blood).

Statistical analysis

Descriptive statistics and univariate relationships were assessed by tabulating adherence status (adherent vs. non-adherent) by patient sociodemographic and clinical characteristics. Percentages were used to describe categorical variables and statistical association was assessed using Fisher's exact test because of small sample size. Multivariable, parsimonious logistic regression models were constructed to predict prophylactic clotting-factor non-adherence (vs. adherence). Factors assessed for their relationship with being adherent included: age, gender, race/ethnicity, parent's education level, bleeding disorder type and severity, and

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history of inhibitor development. Due to the large number of variables collected as part of the survey and because of the small sample size inherent in rare disease research, in addition to the fully adjusted models, final parsimonious models were constructed. In the final parsimonious models, we decided, *a priori*, to include covariates in the model only if they (i) were statistically significant at a two-tailed alpha level of 0.05, (ii) changed the odds ratio of another statistically significant model parameter by at least 10–15% (i.e. confounded) [24], or (iii) improved the precision of another statistically significant parameter already in the model. All statistical analyses were performed using SAS 9.4 (Cary, NC, USA) and STATA 12 (College Station, TX, USA). All *P*-values were calculated using two-sided tests.

Results

Overall, 108 persons aged 13–25 years with haemophilia or VWD participated in the IMPACT QoL study. Thirty-five (32%) participants who reported treating on-demand (i.e. episodically) were excluded from the analysis. The vast majority (95%) of AYAs who self-reported treating their bleeds prophylactically reported that they 'use factor regularly or on a set schedule for prevention' compared to only 5% who reported that they 'use factor before physical activity for prevention.' Of the 73 prophylactically treating AYAs remaining, 88%, 8% and 4% had haemophilia A, B and VWD respectively. Almost all (90%) had severe disease and 58% had never developed an inhibitor. Most were aged 13–17 years (56%), white (78%), non-Hispanic (88%), never married (94%) and had some type of health insurance (96%) (Table 1). Although nearly all respondents were insured, insurance type differed significantly by several factors. Adolescents (vs. young adults) (61% vs. 34%, $P = 0.03$), whites (vs. non-whites) (58% vs. 19%, $P = 0.01$), and respondents whose mothers had at least a bachelor's degree (vs. less than bachelor's) (68% vs. 32%, $P = 0.03$) were significantly more likely to have private/commercial insurance only (vs. public/government insurance, a combination of private and public insurance, or no health insurance). Among respondents, 34% had a mother who completed at least a bachelor's degree and 36% had a father who did so. The education status of the respondents' parents was closely related ($P < 0.01$), and data showed that if a respondent's mother had less than a Bachelor's degree, 85% of the time so too did the father. Likewise, if a respondent's mother had at least a Bachelor's degree, 76% of the time the father did as well.

Median VERITAS-Pro score was 48 (range = 25–78) and 22 (30%) patients were non-adherent (VERITAS-Pro≥57) (Fig. 1). At the univariate level, only age was statistically significantly related to non-adherence to prophylactic treatment regimens, with young adults (aged 18–25 years) having a higher percentage of non-adherence compared to adolescents (aged 13–17 years) (47% vs. 17%, $P = 0.01$) (Table 1) and significantly higher (worse) median VERITAS-Pro scores (54.5 vs. 45.0, $P = 0.01$) (Table 2). Final logistic regression modelling (Table 3) suggested that, compared to those aged 13–17 years, participants aged 18–25 years were 6.2 (95% CI: 1.8–21.0; $P < 0.01$) times more likely to be non-adherent to prescribed prophylactic treatment regimens. The model also revealed that, compared to respondents whose mother had at least a Bachelor's degree, respondents whose mother did not were 3.8 (95% CI: 1.0–14.3; $P = 0.05$) times more likely to be

Table 1. Respondent characteristics by level of adherence as measured by the VERITAS-Pro, 2012 ($n = 73$)*. Values are *n* (%).

Characteristics	Adherent ($n = 51$)	Non-adherent ($n = 22$)	Total ($n = 73$)	Fisher's *P*-value
Age				
13–17	34 (67)	7 (32)	41 (56)	0.01
18–25	17 (33)	15 (68)	32 (44)	
Gender				
Male	51 (100)	21 (95)	72 (99)	0.30
Female	0 (0)	1 (5)	1 (1)	
Race				
White (only)	38 (75)	19 (86)	57 (78)	0.36
Non-White†	13 (25)	3 (14)	16 (22)	
Ethnicity				
Hispanic	8 (16)	1 (5)	9 (12)	0.26
Non-Hispanic	43 (84)	21 (95)	64 (88)	
Health Insurance‡				
Private/Commercial only	28 (55)	8 (36)	36 (49)	0.30
Public/Government only§	12 (24)	6 (27)	18 (25)	
Both Public and Private	2 (4)	4 (18)	6 (8)	
Insured – type unknown	5 (10)	3 (14)	8 (11)	
Uninsured	2 (4)	1 (5)	3 (4)	
Mother's education				
Bachelor's or higher	20 (39)	5 (23)	25 (34)	0.19
Less than Bachelor's	31 (61)	17 (77)	48 (66)	
Father's education				
Bachelor's or higher	18 (35)	8 (36)	26 (36)	0.99
Less than Bachelor's	33 (65)	14 (64)	47 (64)	
Bleeding disorder				
Haemophilia A	46 (90)	18 (82)	64 (88)	0.53
Haemophilia B	3 (6)	3 (14)	6 (8)	
von Willebrand	2 (4)	1 (5)	3 (4)	
Severity				
Mild	1 (2)	0 (0)	1 (1)	0.55
Moderate	3 (6)	3 (14)	6 (9)	
Severe	45 (92)	18 (86)	63 (90)	
Inhibitor development				
Ever	23 (45)	8 (36)	31 (42)	0.61
Never	28 (55)	14 (64)	42 (58)	

*Adherence was assessed using the Validated Haemophilia Regimen Treatment Adherence Scale for prophylactic participants (VERITAS-Pro). The cut-off for non-adherent prophylactic patients was a total VERITAS-Pro score ≥57 as established in ref. [23].

†Most (13/16, 81%) of non-white respondents were black or African American, 2/16 (13%) were Asian and 1/16 (6%) was mixed race.

‡$n = 71$, two respondents answered 'Don't Know' to whether or not they had health insurance and were not included.

§Only two respondents had VA only insurance, the others had Medicaid only.

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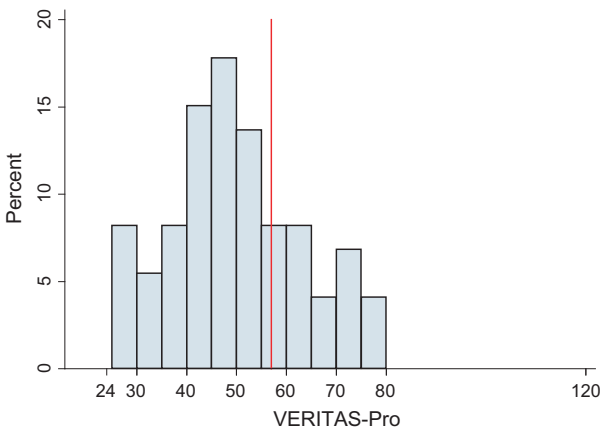

Fig. 1. Percentage distribution of VERITAS-Pro scores, 2012 (n = 73). The red line represents the cut-off for non-adherent prophylactic patients (VERITAS-Pro ≥57) as established by Duncan *et al.* [23]. Median VERITAS-Pro score was 48 (range = 25–78) and 22 (30%) patients were non-adherent (VERITAS-Pro ≥57; to the right of the red line).

non-adherent to prophylaxis. The final parsimonious model also included disease severity, race and ethnicity because they increased the overall precision of the model.

Discussion

Previous studies suggest that as PWH age out of childhood and into adolescence and young adulthood, AYAs often begin taking primary responsibility for their bleeding disorder treatment [13,25]. Subsequently, adherence to prophylaxis regimens frequently worsens [17,26] as the need for prophylaxis is often deprioritized or perceived as unimportant [13]. Further, as children transition into young adulthood, their activity level often intensifies, which could heighten the risk of bleeding.

Results from our study support this theory, but provide even more granularity for this picture – showing that the period of transition from adolescence into young adulthood is a critical time period regarding adherence to prophylaxis. Specifically, although only 17% of participants aged 13–17 years (adolescents) were non-adherent to their prescribed treatment regimens, that proportion nearly tripled to 47% among those aged 18–25 years (young adults). This difference persisted even after controlling for clinical and sociodemographic variables with logistic regression analysis showing that compared to adolescents, young adults were >6 times more likely to be non-adherent to prescribed prophylactic treatment regimens. Reasons behind this are likely complex. Transitioning from adolescence to young adulthood represents a tectonic shift as choices and challenges evolve to include decisions about education or career training, entering the workforce, leaving the family home, managing finances and (sometimes) entering into marriage and parenthood. All of these competing demands – compounded by the fact that, during young adulthood, primary responsibility for bleeding disorder care shifts from the parents to the patient – likely explain much of the difference in adherence to recommended prophylactic treatment regimens between adolescent PWH and young adult PWH that we observed. Indeed, previous research suggests that as many as two-thirds of young adults will experiment with stopping or reducing prophylactic dosing [27]. Subsequently, the case for personalized prophylactic treatment plans for young (and older) adults is gaining momentum [28], and this study underscores the fact that among PWH, targeting the transition period from adolescence to young adulthood is

Table 2. VERITAS-Pro scores by subscale and age group (n = 73).

VERITAS-Pro section	Median	IQR	Mean	Range	SD
All ages (13–25) (n = 73)					
Total scale	48	41–58	49.5	25–78	13.4
Time	8	6–11	8.9	4–20	3.9
Dose	4	4–8	6.1	4–15	2.8
Plan	6	4–9	6.8	4–16	3.0
Remember	9	6–12	9.1	4–18	3.7
Skip	7	5–10	7.7	4–16	3.4
Communicate	10	7–14	10.8	4–20	4.4
Adolescents (13–17) (n = 41)					
Total scale	45	38–54	45.4	25–76	12.7
Time	8	5–10	8.0	4–20	4.0
Dose	4	4–7	5.7	4–12	2.4
Plan	5	4–8	6.3	4–16	2.9
Remember	8	5–10	8.1	4–16	3.5
Skip	7	4–9	7.0	4–16	3.1
Communicate	10	7–14	10.2	4–20	4.1
Young adults (18–25) (n = 32)					
Total scale	54.5	44.5–64.5	54.6	35–78	12.7
Time	10	8–12	10.1	4–20	3.5
Dose	5.5	4–9	6.8	4–15	3.2
Plan	7.5	4.5–9	7.5	4–16	3.1
Remember	11	8–12	10.3	4–18	3.5
Skip	8	5.5–11	8.5	4–16	3.6
Communicate	11.5	7.5–16	11.5	4–19	4.7

Possible subscale scores ranged from four points (most adherent) to 20 (least adherent), and possible total scores ranged from 24 (most adherent) to 120 (least adherent).

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) of being non-adherent as measured by the VERITAS-Pro, 2012 (n = 73).*,†

Characteristics	OR (95% CI)	P-value
Age		
18–25	6.16 (1.81, 21.0)	<0.01
13–17	1.00	
Mother's education		
Less than Bachelor's	3.77 (1.00, 14.3)	0.05
Bachelor's or higher	1.00	

*Adherence was assessed using the Validated Haemophilia Regimen Treatment Adherence Scale for prophylactic participants (VERITAS-Pro). The cut-off for non-adherent prophylactic patients was a total VERITAS-Pro score ≥57 as established in ref. [23].
†The model was also adjusted for disease severity and race/ethnicity.

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important for maintaining adequate haemophilia treatment across the life course. Finally, it may also be that case that transitioning into young adulthood means leaving the health insurance coverage once provided by one's parents and having to obtain health insurance coverage independently. While health insurance status/type did not ultimately predict adherence in our study after adjustment for age, young adults (vs. adolescents) (34% vs. 61%, $P = 0.03$) were much less likely to rely exclusively on private/commercial health insurance for coverage, and were more likely to rely upon public/government health insurance (e.g. Medicaid) or be uninsured. Future studies should continue to evaluate the impact of health insurance status among young adults who are managing a bleeding disorder.

A second finding from this study was that prophylactic adherence was worse for AYAs whose mothers have less formal education. Specifically, compared to respondents whose mother had at least a Bachelor's degree, respondents whose mother did not were nearly four times more likely to be non-adherent to prescribed prophylactic treatment regimens. This finding is novel and supports previous research that suggests better knowledge about one's bleeding disorder and the importance of treatment is related to improved adherence [12,13,16,18]. This finding also suggests that healthcare providers should dedicate adequate time and resources to family adherence education, and that, especially for AYAs, adherence efforts go beyond the patient and extend to family members and other social support members.

Previous work about increasing adherence among AYA PWH has suggested that effective strategies might also include designing individualized prophylactic treatment regimens around 'risk periods' (e.g. sporting events and other physical activity or time away from home), focusing on 'wellness' instead of 'adherence' *per se*, and recognizing health as a 'state of doing' and not a 'state of being', thereby integrating the bleeding disorder into everyday life instead of allowing the disease to become a burden [29]. Other research has suggested that it is important for PWH to alter the treatment paradigm from a victimized state where the infusion is something you do *to* yourself, to an empowerment state where the infusion is something you do *for* yourself [30]. These approaches, which stemmed from research in AYA PWH, are similar to earlier research in other (non-haemophilia) AYA chronic disease states that suggest motivation, a sense of normality, experience of results, and parental support and encouragement all lead to increased compliance [31].

This study has limitations. Primarily, data were cross sectional, thus causal inference cannot be made. For example, although study results support that AYA PWH whose mothers have less formal education tend to have worse adherence, the directionality of this relationship cannot be confirmed. That is, it is also possible that AYAs who maintain adherence to prophylaxis need less medical attention, thereby providing a better climate for their parents to pursue college education. This cannot be teased out in a cross-sectional study and should be examined in the future with prospective research. A second limitation is that all data were self-reported. As such, information about blood disorder type and severity, health insurance coverage, and other demographic, clinical and behavioural information are not confirmed by medical record review or administrative claims data. However, by obtaining data through self-report, this study was able to collect important, reliable and valid patient-report outcome data about adherence. Finally, AYA PWH were primarily recruited from large national or regional haemophilia meetings. Thus, our convenience sample of AYA PWH may not adequately represent the broader AYA PWH population who do not typically attend these meetings. Despite these limitations, this is the first study to best of our knowledge to analyse predictors of adherence to prescribed prophylactic clotting-factor treatment regimens among AYAs using a standardized and validated patient-reported measure of adherence.

Conclusion

Previous research suggests that among AYAs with a bleeding disorder, better adherence to clotting-factor treatment regimens is associated with less chronic pain and the preservation of joint health and QoL [3,8–11]. Results from this study suggest that adherence efforts should be especially targeted to young adults as they transition from adolescence (i.e. parental supervision) and assume primary responsibility for their bleeding disorder care. Finally, healthcare providers should be especially mindful of AYAs whose mothers have less formal education and ensure that adequate time and resources are dedicated to family adherence education.

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Disclosures

Drs McLaughlin, Anderson and Tortella are employees and shareholders of Pfizer Inc. Mr Munn is a member of Nurse Advisory Board for Baxter, Biogen-Idec, CSL Behring, NovoNordisk and Pfizer. He received a consulting fee from Bayer and was a speaker for Novo Nordisk. Dr Witkop and Mrs Lambing stated that they had no interests which might be perceived as posing a conflict or bias at the time the study was conducted.

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