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ORIGINAL ARTICLE

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Hemophilia prophylaxis adherence and bleeding using a tailored, frequency-escalated approach: The Canadian Hemophilia Primary Prophylaxis Study

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Abstract

Background: Standard of care for persons with severe hemophilia A includes regular replacement of factor VIII (FVIII). Prophylaxis regimens using standard half-life (SHL) FVIII concentrates, while effective, are costly and require frequent intravenous infusions.

Aim: This study evaluated the adherence of 56 boys with severe hemophilia A to tailored, frequency-escalated prophylaxis with an SHL recombinant FVIII concentrate.

Methods: We reviewed the factor infusion and bleeding logs of study subjects. Adherence to the prescribed regimen was calculated on a weekly basis, and bleeding rates were determined from self/proxy-reported bleeding logs. The primary outcome was adherence to the prescribed prophylaxis regimen.

Results: The median (range of values [ROV]) weekly adherence to prophylaxis was 85.7% (37.4%-99.8%). The median (ROV) adherent weeks on steps 1 (weekly), 2 (twice weekly), and 3 (alternate-day) were 92.9% (50%-100%), 80.3 (32%-96%), and 72.6% (14%-98%); relative to step 1, subjects were less likely to be adherent on steps 2 and 3 ($P < 0.00$). On step 1, our cohort had higher adherence than previously reported rates. The median (ROV) adherence to the breakthrough bleeding protocol was 47.1% (0%-100%). At any given time, bleeding risk was reduced by 15% for each 10% increase in adherence during the preceding 12 weeks (hazard ratio, 0.85; 95% confidence interval, 0.81-0.90).

Conclusion: This cohort had high rates of adherence to the prescribed prophylaxis regimen. Initiating prophylaxis with once-weekly infusions facilitated adherence to the prophylaxis regimen in this cohort of boys with severe hemophilia A started on primary prophylaxis at a very young age.

KEYWORDS

bleeding, factor VIII, hemophilia A, prophylaxis, treatment adherence and compliance

Essentials

- Prophylaxis adherence is an important factor contributing to long-term joint health in boys with hemophilia.
- This study analyzed adherence rates in the Canadian Hemophilia Primary Prophylaxis Study cohort.
- Adherence to prophylaxis was high but decreased as infusion frequency increased.
- Bleeding incidence was reduced if a subject was adherent in the preceding 12 weeks.

1 | INTRODUCTION

Prophylaxis for severe hemophilia is more effective than on-demand therapy for the treatment of severe hemophilia,[1] but there is no agreed-upon optimal prophylaxis regimen.[2,3] The Canadian Hemophilia Prophylaxis Study (CHPS) group previously examined the cost-effectiveness of a tailored, frequency-escalated prophylaxis regimen.[4] This form of prophylaxis is generally less costly than full-dose prophylaxis.[5]

Despite the growing practice of prescribing prophylaxis, adherence to the prophylaxis regimen is required for benefit, regardless of which prophylaxis regimen is used. In severe hemophilia, sustained adherence to factor replacement therapy is required to prevent recurrent spontaneous bleeding into muscles and joints due to the relatively short half-life of standard plasma-derived or recombinant clotting factor products.[6]

A global definition of *adherence*, as it relates to medication, does not exist.[7,8] The World Health Organization has adopted a broad definition for adherence, calling it the "extent to which a person's behavior … corresponds with agreed recommendations from a health care provider."[9] This broad definition is because standards for adequate adherence are highly disease dependent. For example, HIV-infected individuals with medication adherence levels <95% experience a poor response to treatment, whereas individuals with conditions such as diabetes or asthma can achieve satisfactory symptom control at adherence rates of 40% to 60%.[9]

For hemophilia, there is no evidence-based threshold for what should be considered adequate adherence to a recommended prophylaxis regimen. There is, however, evidence to suggest that the threshold should be high; previous work has shown that even limited nonadherence can result in irreversible joint damage.[10]

Unfortunately, high levels of adherence are often difficult to maintain, especially for the treatment of chronic conditions.[9] Factor VIII (FVIII) and IX (FIX) replacement therapy, as is currently prescribed, involves regular intravenous infusions of clotting factor, which can be challenging for reasons that include needle aversion and difficult venous access, particularly in very young boys started on programs of primary prophylaxis.[11,12]

The CHPS was a single-arm, multicenter prospective study designed to investigate the efficacy of a tailored, frequency-escalated, primary prophylaxis regimen.[13] This current substudy had 2 objectives: first, to describe the treatment adherence rates for CHPS participants and determine if the frequency-escalated approach resulted in better adherence than is reported in the literature and

second, to examine the relationship between treatment adherence and bleeding episodes. Specifically, we sought to confirm the theorized strong relationship between adherence and bleeding.

2 | METHODS

2.1 | Study design

The CHPS was an inception cohort of 56 young boys with severe hemophilia A, defined by a circulating FVIII level of <2%. Detailed descriptions of the study design have been previously reported.[13,14] For the current analysis, we assessed the factor infusion and bleeding logs of all 56 boys on study from 1997 to 2013. Six subjects were lost to follow-up over the course of the 15-year follow-up period.

2.2 | Inclusion and exclusion criteria

The detailed inclusion and exclusion criteria of the CHPS have been previously reported.[13,14] Briefly, subjects were between 12 and 30 months of age at the time of enrollment, with normal joints on radiologic examination, no clinically significant bleeding history, and no present or past history of an FVIII inhibitor. Subjects were not enrolled if they had ≥3 bleeds into any 1 joint, a history of inhibitor, or a competing disease such as hepatitis C.

2.3 | Tailored, frequency-escalated prophylaxis protocol

Subjects enrolled in the CHPS were treated with 3 treatment steps and specific criteria for escalation (Table 1). All patients were started on step 1, 50 IU/kg of body weight of recombinant standard half-life FVIII (rFVIII) concentrate given intravenously once per week. When escalation criteria were met, patients were escalated to step 2 (30 IU/kg twice per week), then to step 3 (25 IU/kg on alternate days or at least 3 times per week). While the method of administration of prophylaxis doses was not dictated as part of the study, the once-weekly doses were started in the hospital, with patients moving to home care as soon as was feasible. Following a joint or significant soft tissue bleed, the prophylaxis regimen was augmented by an enhanced, episodic (on-demand) treatment schedule, which consisted of a 40 IU/kg infusion of rFVIII at the time of a bleeding episode and additional doses of 20 IU/kg on the first and third days following the bleed. All dosing was rounded up to the nearest vial size.

TABLE 1 Dose and escalation criteria for the tailored, frequency-escalated, prophylaxis approach used in the CHPS

Dose regimen	Escalation criteria
Step 1:50 IU/kg[a] 1×/wk	≥3 bleeds into any single joint over a consecutive 3-mo period; **or**
Step 2:30 IU/kg[a] 2×/wk	≥4 significant soft tissue or joint bleeds (into any number of joints) over a consecutive 3-mo period; **or**
Step 3:25 IU/kg[a], alternate days, minimum 3×/wk	≥5 bleeds into any single joint while on the same dose of factor therapy

[a]Rounded to the nearest vial size.

2.4 | Measuring adherence

Adherence to the prescribed prophylaxis regimen was calculated on a weekly basis. A given week was considered adherent if the subject completed all of their infusions as per their prescribed step on the protocol; infusions given beyond the number required were not included when determining adherence to prophylaxis so that no patient could have an adherence rate of >100%. Similar rates were also calculated for adherence to the prescribed enhanced episodic treatment schedule. This information was collected from each subject's infusion log.

Bleeding rates were collected from the subject's self- or proxy-reported bleeding logs. Bleeding and treatment for bleeding were recorded by parents, guardians, or the participants themselves and confirmed by study personnel at each study visit (every 3 months for the first 5 years of the study, then every 6 months). The bleeding episodes were classified by study staff as index hemarthroses (ie, bleeds into ankles, elbows, or knees), other hemarthroses, muscle bleeds, superficial bleeds, mucosal bleeds, or life-threatening bleeds (eg, intracranial or airway bleeding).

2.5 | Outcome

The primary outcome was adherence to the prescribed prophylaxis regimen and how the adherence in our cohort compared to previously reported adherence rates. Secondary outcomes included adherence to the enhanced episodic therapy protocol and bleeding rates.

2.6 | Literature review

We conducted a search of the literature in MEDLINE, using the following MeSH terms: *compliance*, *treatment adherence and compliance*, *adherence*, *medication adherence*, *FVIII*, *hemophilia A*, *hemophilia B*, *Factor IX*, and *hemophilia*, limited to pediatric cohorts and published before April 30, 2019. A single reviewer reviewed titles and abstracts and selected papers for full text review if the population included pediatric patients and adherence rates were reported. Population characteristics, reported definitions of adherence, adherence rates, and any other relevant information on how the authors described adherence were abstracted and qualitatively summarized.

2.7 | Statistical analysis

We used descriptive statistics (median, range of values [ROV]) to describe the cohort and their adherence rates. We calculated 95% confidence intervals (CIs) on reported adherence data found in the literature review using either the published median and sample size, or mean, standard deviation, and sample size. Due to the variability in the way adherence was defined and reported, we compared our rates and confidence interval bands qualitatively to those reported in the literature.

The association between having a central venous access device (CVAD) and adherence was determined using a generalized linear mixed-effects model, with a logistic link function and random intercept, adjusting for the time spent in each step of the protocol.

The relationship between adherence and bleeding was determined through a recurrent event analysis using a Cox proportional hazards model with robust standard errors, controlling for age and step of the protocol. We defined each risk period as Monday through Sunday of a given week to infer whether a patient would have bled during that week based on their average weekly adherence to the prescribed prophylaxis regimen over the previous 12 weeks. We chose to look at adherence for the 12 weeks prior to the event week to provide a stable representation of adherence over time, and because the infusion diaries and bleed logs were collected every 12 weeks for the first 5 years of the study. We performed a sensitivity analysis using varying time frames for average adherence (over the preceding 2 and 6 weeks) to test the robustness of the relationship. We included all available data in our analysis, including data from subjects who were lost to follow-up.

We performed a sensitivity analysis of our primary model using 4 scenarios for weeks with missing bleed or adherence data. For these analyses, we separately assumed that weeks with missing adherence data were either all adherent or all nonadherent (ie, all 1 or 0), and that weeks with missing bleed data were either all bleeding weeks or all nonbleeding weeks (ie, all 1 or 0).

We also performed an exploratory analysis using multiple linear regression to investigate which factors might be predictive of end-of-study joint damage as determined by the magnetic resonance imaging (MRI) 17-point International Prophylaxis Study Group (IPSG) scores or the Hemophilia Joint Health Scores (HJHS) (both previously described[13]). The covariates that were considered in this analysis were overall adherence to prophylaxis, adherence to the enhanced episodic therapy following bleeds, annualized index joint bleeding rate, and the age at first joint bleed.

We conducted all analyses using R version 3.5.0 [15].

3 | RESULTS

3.1 | Sample

Fifty-six boys with severe hemophilia A were followed as part of the CHPS cohort for a median (ROV) of 10.2 (0.2-16.1) years (Table 2). This represents a median (ROV) of 506 (10-841) weeks of infusion diaries and bleeding logs. There was a median (ROV) of 3.9% (0%-27.6%) of weeks missing per subject.

3.2 | Adherence

In our cohort, the overall median (ROV) adherence with prophylaxis was 85.7% (37.4%-99.8%) weeks per subject. The median (ROV) adherent weeks on steps 1, 2, and 3 were 92.9% (50.0%-100%), 80.3% (32.0%-96.0%), and 72.6% (14.0%-98.0%), respectively. Relative to step 1, subjects were less likely to be adherent on steps 2 and 3 (odds ratio [OR], 0.27; 95% CI, 0.25-0.28; and OR, 0.21; 95% CI, 0.19-0.22, respectively). Subjects with a CVAD were more likely to be adherent on any given week while the device was in place (OR, 1.18; 95% CI, 1.12-1.25). The median (ROV) adherence with the enhanced episodic

TABLE 2 Baseline demographic and clinical characteristics of the CHPS cohort

Characteristic	Participants (N = 56)
Median age at enrollment, y (ROV)	1.63 (1-2.5)
Family history of hemophilia, n (%)	
Yes	18 (32)
No	38 (68)
Genotype, n (%)	
Null mutation[a]	43 (77)
Non-null mutation[b]	6 (11)
Unknown	7 (12)
CVAD placed prior to study entry, n (%)	56 (100)
Yes	15 (26.8)
No	41 (73.2)
No inhibitor at baseline, n (%)	56 (100)
Enrollment center, n (%)	
Hamilton	10 (17.9)
Montreal	10 (17.9)
Winnipeg	9 (16.1)
Toronto	8 (14.3)
Calgary	7 (12.5)
Quebec City	5 (8.9)
Ottawa	2 (3.6)
Saskatoon	2 (3.6)
Halifax	1 (1.8)
Thunder Bay	1 (1.8)
Vancouver	1 (1.8)

[a]Defined by intron 22 and intron 1 inversions, nonsense mutations, large deletions, small deletions/insertions outside poly-A runs, or splice-site mutations involving conserved nucleotides.[33]

[b]Defined by missense mutations, small deletions/insertions within poly-A runs, or splice-site mutations involving nonconserved nucleotides[33].

therapy protocol (ie, following an index joint or muscle bleed [see above]) was 47.1% (0%-100%) per subject.

Our literature search for reported adherence rates identified 232 articles. Abstracts and titles were reviewed by one of the authors (SD), and 15 manuscripts were retrieved that reported adherence rates for a cohort that included pediatric patients. Results are summarized in Table 3; where the cohort included both pediatric and adult populations, only the pediatric results are presented.

In the articles retrieved, there was a high degree of variability in how adherence was defined and reported, which made it impossible to combine studies for meta-analysis. However, we did find that our cohort, at a median 92.9% (95% CI, 86.2%-99.6%) adherent weeks per subject, had higher adherence while on step 1 of our tailored frequency-escalated protocol than any other reported adherence rates, whether objective or subjective. This was higher than the upper confidence bounds reported in 7 of 10 manuscripts where a 95% CI could be calculated from the published data. Our overall adherence rate of 85.7% (95% CI, 76.5%-94.9%) adherent weeks was also either within (for 5/10 studies) or above (for 5/10 studies) the confidence bounds of the other reported adherence rates.

3.3 | Bleeding

Adherence was strongly associated with a decreased risk of bleeding, after accounting for age (Table 4). A 10% increase in the absolute adherence rate over any 12-week period was associated with a 15% reduction in bleeding rate (hazard ratio [HR] 0.85; 95% CI, 0.81-0.90). The observed effect diminished slightly as the prophylaxis step increased, but the association remained strong and highly significant. Our sensitivity analysis of varying adherence time frames showed, in fact, a stronger relationship between adherence and bleeding than we observed when analyzing the average adherence over 12 weeks (as the adherence time frame got smaller, the HR decreased as well; Table S1). Our sensitivity analysis, to account for missing data, showed similar HRs (Table S2).

3.4 | Joint health

The only statistically significant predictive model for end-of-study total MRI score included adherence rate (estimate, 20.27; standard error [SE], 12.36) and annualized joint bleeding rate (estimate, 3.71; SE, 1.35). The results of the regression indicated that these 2 covariates explained 15% of the variance (R^2 = 0.15; $F(2,43)$ = 3.79; P = 0.03) in the total MRI score. There were no statistically significant predictors for the end of study HJHS score.

4 | DISCUSSION

Our results show that adherence rates for subjects on a tailored, frequency-escalated primary prophylaxis regimen were high. Our median adherence level of over 85% is consistent with other reported cohorts, including a survey of 6 European countries that reported adherence rates in the 80% to 87% range[16] and an Australian summary of real-world prophylaxis use that reported a majority of patients in the "optimal" adherence range of 75% to 125% of expected clotting factor concentrate use.[17]

However, the median adherence level from step 1 of our prophylaxis regimen of almost 93% was higher than has previously been reported.[10,11,16–28] The reduced number of infusions, especially in the early years of prophylaxis, and the increased likelihood of infusions in a hospital setting may have contributed to increased adherence. High adherence to a lower number of infusions may help boys and their families establish good infusion habits, as making small, incremental changes is often an important factor in forming lasting health-related habits.[29] This also becomes relevant with the advent of extended half-life clotting factor concentrates, as once-weekly infusions are likely to provide sufficient coverage to prevent spontaneous bleeding.[30]

Our results show that adherence to the enhanced episodic therapy following a joint bleed was moderate, at almost 50%. This component of the CHPS protocol was identical to the enhanced episodic treatment arm in the prospective joint outcome study (JOS) reported by Manco-Johnson et al[1]; the rationale for the enhanced episodic treatment protocol in both the JOS and CHPS was to provide adequate hemostatic cover during the period of recovery from an acute joint bleed, thus potentially reducing the risk for rebleeding and the development of a target joint. This could explain to some extent why, at the individual level, some boys over time manifested clinically significant joint disease as measured by MRI. We previously reported that end-of-study imaging outcomes were good overall but that some individuals had evidence of significant joint damage with individual joint scores on the 17-point IPSG MRI scale as high as 14 (on this scale, a score of 17 indicates maximal damage per index joint).[13]

The subjects who had a CVAD for some period of time during the study demonstrated increased adherence during the time when infusions were administered via the CVAD compared to the time when infusions were given via peripheral venipuncture. This may be because accessing a CVAD for a home-infusion is easier for parents or caregivers, and difficult peripheral venous access may lead to multiple attempts and ultimately missed infusions. Additionally, in many cases, a parent or caregiver was the one giving infusions via a CVAD, whereas peripheral venous infusions may have been more likely to be self-administered, especially as the boys got older, which may account for the lower adherence.

We found that adherence to the prophylaxis regimen in the previous 12 weeks was associated with a decreased risk of bleeding at any given time. The effect was strongest for subjects infusing once weekly (ie, those on step 1) and decreased slightly as the frequency of infusions increased. This was not surprising, as adherence is most important when receiving only 1 infusion/week, as missing that single infusion would leave a patient unprotected for several days, compared to ≥2 infusions/week where missing

TABLE 3 Summary of previously reported adherence definitions and rates for pediatric cohorts of subjects with either hemophilia A or B

Reference number	Definition of adherence	Sample size	Reported results	Calculated 95% confidence interval
10	Percentage of adherent weeks, with adherent week defined as a week where between 80% and 150% of prescribed units are given and <33% is low, 34%-66% is moderate and 67%-100% is high adherence	19	26% of patients have high adherence	6%-46%
11	No definition of adherence given	34	58.8% of survey respondents self-reported that they had "excellent" adherence	42.3%-75.3%
16	Percentage of factor concentrate administered relative to the amount prescribed	180	80%-87% of factor administered	NA
17	Ratio of observed to expected factor usage; optimal adherence defined as infusing between 75%-125% of prescribed factor	453	65.8% of patients with optimal adherence to prophylaxis	61.5%-70.2%
18	Percentage of weeks per year that the patient was adherent to the infusion frequency of the prescribed prophylaxis regimen	14	Median (IQR) of 86% (75%-91%) of adherent weeks per subject	68%-104%
19	Weekly adherence with prescribed infusion frequency	16	Median (IQR) of 88.6% (73.2%-96.9%) of adherent weeks per subject	73.0%-104.2%
20	Adherence defined as missing <15% of prescribed infusions (adherence rate ≥85%)	73	66% of patients were adherent	55%-77%
21	Percentage of time periods (180 d) where supply of product administered (obtained from pharmacy database) was ≥60% of supply ordered	74	Mean of 51% (SD, 36%) adherent time periods	43%-59%
22	Percentage of patients who had ≥75% adherence to prescribed regimen, based on IU dispensed/total IU required for regimen (based on pharmacy database)	52	73.1% of patients ≥75% adherence Mean adherence of 85.7% (SD, 23.8%) calculated from pharmacy records (IU dispensed/IU required)	79.3%-92.2%
23	Percentage of prescribed daily dose received for patients on daily low-dose prophylaxis	17	Median, 85% (range, 56%-98%)	68%-102%
24	Adherence index defined as units administered/units prescribed, then subtracted from 100 to determine the difference (over or under) from perfect adherence	78	Mean, −3.1 (SD, 14.4) with a range of −64.4 to 66.7	−6.3 to 0.1
25	Used VERITAS-PRO[a] questionnaire	55	Mean score, 39.6 (SD, 11.7)	NA
26	Used VERITAS-PRO[a] questionnaire	69	Mean score, 49.6 (SD, 12.9) with a range of 25-78	NA
27	Used VERITAS-PRO[a] with defined cutoff of ≥51 indicating nonadherence	78	18% of patients had score of ≥51 indicating nonadherence	NA
28	No definition of adherence given	22	73% of patients had "excellent" adherence to a prophylaxis regimen	54%-92%

IQR, interquartile range; NA, not applicable; SD, standard deviation.

[a]Validated Hemophilia Regimen Treatment Adherence Scale—Prophylaxis with a score range of 24-120, with 24 representing perfect adherence to prophylaxis.[34]

TABLE 4 Relationship between adherence and risk of bleeding

Step of protocol	Hazard ratio	95% CI
Step 1	0.78	0.70-0.85
Step 2	0.83	0.78-0.88
Step 3	0.82	0.75-0.90
Overall	0.85	0.81-0.90

Note: The hazard ratio represents the reduction in bleeding rate associated with 10% (additive) increase in adherence over any given 12-wk period. The hazard ratios show a reduction of the bleeding rate, which is true across all protocol treatment steps, but diminished as prophylaxis step increased.

an infusion would still provide a better level of coverage. This association provides evidence for the theorized strong relationship between adherence and bleeding; when a person with hemophilia is compliant with their prophylaxis regimen, their risk of spontaneous bleeding is reduced.[6,31]

4.1 | Limitations

Our data are based on self-reported infusion and bleeding logs. We know from previous work that boys with hemophilia/their families sometimes have difficulty determining if a bleeding episode has occurred.[32] Despite this, in the absence of imaging, self- or proxy reporting of bleeding episodes is the standard of practice across hemophilia treatment centers. Where possible in this prospective study, a multidisciplinary team consisting of hematologists, physical therapists, nurse practitioners, and hematology nurses confirmed reported bleeding episodes following discussion with the boys and/or their parents/guardians, and a review of the subjects' treatment logs.

Our cohort of patients had very high adherence rates and very low bleeding rates. It is possible that the association between adherence and bleeding seen in our cohort would be even stronger for a group of patients where adherence was lower, and there would likely have been more bleeding events. Although there were some missing data from the subjects' logs, the sensitivity analysis showed that the effect of the missing data was negligible.

It is possible that the cohort of patients who enrolled in the study may have been more likely to be adherent to their therapy than the general hemophilia population. For the CHPS, we excluded patients and families thought to be nonadherent based on the assessment of the local investigator at each site. During the recruitment period, 14 patients were excluded for this reason. While no specific strategies were used to encourage adherence as part of the study protocol, this exclusion criterion may have affected our adherence rates. However, our results showed a correlation between bleeding and adherence, and had we had more patients whose adherence was lower, we would have seen a larger effect.

Finally, one of our study patients was on study for only a very short period of time. Removing this subject did not affect any of the results (data not shown), so this patient was left in, as we included all patients with available data in all analyses.

5 | CONCLUSION

Overall, the adherence rates for subjects on tailored frequency-escalated primary prophylaxis were high, and starting the cohort on once-weekly infusions resulted in adequate factor coverage while maintaining an above-average adherence level. Higher adherence rates were associated with a marked reduction in risk of bleeding at any given time. Moreover, adherence likely plays a definable role in determining long-term joint outcomes in patients with severe hemophilia.

RELATIONSHIP DISCLOSURE

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AUTHOR CONTRIBUTIONS

SD assisted in the data analysis and interpretation and wrote the first draft of the manuscript. VSB assisted in the design of the study, was co–principal investigator, assisted in the analysis and interpretation of the data, and critically revised the manuscript. DW conducted the data analysis and critically revised the manuscript. E Pullenayegum assisted with the data analysis and interpretation and critically revised the manuscript. DK assisted in the data analysis and critically revised the manuscript. BS assisted in the data analysis and critically revised the manuscript. SAH, SC, GER, RJK, NL, AKC, SJI, RS, MS, and JKW critically revised the manuscript. BMF assisted in the design of the study, was co–principal investigator, assisted in the analysis and interpretation of the data, and critically revised the manuscript.

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REFERENCES

1. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med. 2007;357:535–44.
2. Lee C, Kessler C, Varon D, Martinowitz U, Heim M, Ljung R. Prophylactic treatment in Sweden—overtreatment or optimal model? Haemophilia. 1998;4:409–12.
3. Lee C, Kessler C, Varon D, Martinowitz U, Heim M, Szucs T, et al. Resource utilisation in haemophiliacs treated in Europe: results from the European Study on Socioeconomic Aspects of Haemophilia Care. Haemophilia. 1998;4:498–501.
4. Abrahamyan L, Willan AR, Beyene J, Mclimont M, Blanchette V, Feldman BM. Using value-of-information methods when the disease is rare and the treatment is expensive—the example of hemophilia A. J Gen Intern Med. 2014;29:767–73.
5. Bohn RL, Avorn J, Glynn RJ, Choodnovskiy I, Haschemeyer R, Aledort LM. Prophylactic use of factor VIII: an economic evaluation. Thromb Haemost. 1998;79:932–7.
6. Schrijvers L, Uitslager N, Schuurmans M, Fischer K. Barriers and motivators of adherence to prophylactic treatment in haemophilia: a systematic review. Haemophilia. 2013;19:355–61.
7. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487–97.
8. Lehane E, McCarthy G. Medication non-adherence—exploring the conceptual mire. Int J Nurs Pract. 2009;15:25–31.
9. Sabaté E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
10. Du Treil S, Rice J, Leissinger C. Quantifying adherence to treatment and its relationship to quality of life in a well-characterized haemophilia population. Haemophilia. 2007;13:493–501.
11. Hacker M, Geraghty S, Manco-Johnson M. Barriers to compliance with prophylaxis therapy in haemophilia. Haemophilia. 2001;7:392–6.
12. Fischer K, Collins P, Ozelo M, Srivastava A, Young G, Blanchette V. When and how to start prophylaxis in boys with severe hemophilia without inhibitors: communication from the SSC of the ISTH. J Thromb Haemost. 2016;14:1105–9.
13. Feldman BM, Rivard GE, Babyn P, Wu JK, Steele M, Poon M-C, et al. Tailored frequency-escalated primary prophylaxis for severe haemophilia A: results of the 16-year Canadian Hemophilia Prophylaxis Study longitudinal cohort. Lancet Haematol. 2018;5:e252–e260.
14. Feldman B, Pai M, Rivard G, Israels S, Poon MC, Demers C, et al. Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study. J Thromb Haemost. 2006;4:1228–36.
15. R Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2018.
16. De Moerloose P, Urbancik W, Van Den Berg H, Richards M. A survey of adherence to haemophilia therapy in six European countries: results and recommendations. Haemophilia. 2008;14:931–8.
17. Mason J, Parikh S, Tran H, Rowell J, McRae S. Australian multicentre study of current real-world prophylaxis practice in severe and moderate haemophilia A and B. Haemophilia. 2018;24:253–60.
18. Lock J, Raat H, Peters M, Scholten M, Beijlevelt M, Oostenbrink R, et al. Optimization of home treatment in haemophilia: effects of transmural support by a haemophilia nurse on adherence and quality of life. Haemophilia. 2016;22:841–51.
19. Lock J, Raat H, Duncan N, Shapiro A, Beijlevelt M, Peters M, et al. Adherence to treatment in a Western European paediatric population with haemophilia: reliability and validity of the VERITAS-Pro scale. Haemophilia. 2014;20:616–23.
20. Schrijvers LH, Beijlevelt-van der Zande M, Peters M, Lock J, Cnossen MH, Schuurmans MJ, et al. Adherence to prophylaxis and bleeding outcome in haemophilia: a multicentre study. Br J Haematol. 2016;174:454–60.
21. Armstrong EP, Malone DC, Krishnan S, Wessler MJ. Adherence to clotting factors among persons with hemophilia A or B. Hematology. 2015;20:148–53.
22. Pérez-Robles T, Romero-Garrido JA, Rodriguez-Merchan EC, Herrero-Ambrosio A. Objective quantification of adherence to prophylaxis in haemophilia patients aged 12 to 25 years and its potential association with bleeding episodes. Thromb Res. 2016;143:22–7.
23. Mizrahi T, St-Louis J, Young NL, Ménard F, Zourikian N, Dubé E, et al. Adherence to treatment regimen and bleeding rates in a prospective cohort of youth and young adults on low-dose daily prophylaxis for severe hemophilia A. BMC Hematol. 2016;16:26.
24. García-Dasí M, Aznar J, Jiménez-Yuste V, Altisent C, Bonanad S, Mingot E, et al. Adherence to prophylaxis and quality of life in children and adolescents with severe haemophilia A. Haemophilia. 2015;21:458–64.
25. Krishnan S, Vietri J, Furlan R, Duncan N. Adherence to prophylaxis is associated with better outcomes in moderate and severe haemophilia: results of a patient survey. Haemophilia. 2015;21:64–70.
26. McLaughlin J, Witkop M, Lambing A, Anderson T, Munn J, Tortella B. Better adherence to prescribed treatment regimen is related to less chronic pain among adolescents and young adults with moderate or severe haemophilia. Haemophilia. 2014;20:506–12.
27. van Os SB, Troop NA, Sullivan KR, Hart DP. Adherence to prophylaxis in adolescents and young adults with severe haemophilia: a quantitative study with patients. PLoS ONE. 2017;12:e0169880.
28. Thornburg C, Pipe SW. Adherence to prophylactic infusions of factor VIII or factor IX for haemophilia. Haemophilia. 2006;12:198–9.
29. Gardner B, Lally P, Wardle J. Making health habitual: the psychology of 'habit-formation'and general practice. Br J Gen Pract. 2012;62:664–6.
30. Konkle BA, Shapiro A, Quon D, Staber J, Suzuki T, Poloskey S, et al. BIVV001: The first investigational factor VIII therapy to break through the VWF ceiling in hemophilia A, with potential for extended protection for one week or longer. Blood. 2018;132:636.
31. Manco-Johnson MJ, Soucie JM, Gill JC. Prophylaxis usage, bleeding rates and joint outcomes of hemophilia 1999–2010: a surveillance project. Blood. 2017;129:2368–74.
32. Kidder W, Nguyen S, Larios J, Bergstrom J, Ceponis A, von Drygalski A. Point-of-care musculoskeletal ultrasound is critical for the diagnosis of hemarthroses, inflammation and soft tissue abnormalities in adult patients with painful haemophilic arthropathy. Haemophilia. 2015;21:530–7.
33. Carcao MD, van den Berg HM, Ljung R, Mancuso ME. Correlation between phenotype and genotype in a large unselected cohort of children with severe hemophilia A. Blood. 2013;121:3946–52.
34. Duncan N, Kronenberger W, Roberson C, Shapiro A. VERITAS-Pro: a new measure of adherence to prophylactic regimens in haemophilia. Haemophilia. 2010;16:247–55.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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