CLINICAL RESEARCH

Predictors of treatment adherence in patients with chronic disease using the Multidimensional Adherence Model: unique considerations for patients with haemophilia

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Adherence to prophylaxis among people with haemophilia is known to be variable. A retrospective study of patients treated at an urban haemophilia treatment centre in Canada suggests there may be predictors of adherence beyond the WHO's inclusive Multidimensional Adherence Model.

Introduction: Adherence to treatment recommendations in patients with chronic disease is complex and is influenced by numerous factors. Haemophilia is a chronic disease with reported levels of adherence ranging from 17–82%. **Aim:** Based on the theoretical foundation of the World Health Organization Multidimensional Adherence Model, the objective of this study was to identify the best combination of the variables infusion frequency, annualised bleed rate, age, distance to haemophilia treatment centre (HTC) and Haemophilia Joint Health Score (HJHS), to predict adherence to treatment recommendations in patients with haemophilia A and B on home infusion prophylaxis in Canada. **Methods:** A one-year retrospective cohort study investigated adherence to treatment recommendations using two measures: 1) subjective report via home infusion

diaries, and 2) objective report of inventory ordered from Canadian Blood Services. Stepwise regression was performed for both measures. **Results:** Eighty-seven patients with haemophilia A and B, median age 21 years, were included. Adherence for both measures was 81% and 93% respectively. The sample consisted largely of patients performing an infusion frequency of every other day (34%). Median scores on the HJHS was 10.5; annualised bleed rate was two. Distance to the HTC was 51km. Analysis of the objective measure weakly supported greater infusion frequency as a treatment-related factor for the prediction of lower adherence, however the strength of this relationship was not clinically relevant (R2=0.048). For the subjective measure, none of the explanatory variables were significant. **Conclusion:** Adherence is a multifaceted construct. Despite the use of theory, most of the variance in adherence to treatment recommendations in this sample of patients with haemophilia remains unknown. Further research on other potential predictors of adherence, and possible variables and relationships within factors of the MAM is required.

The World Health Organization (WHO) defines adherence as "the extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"[1]. The WHO suggests that improving adherence to treatment recommendations for patients with chronic disease may have a greater impact on patient outcomes than any improvement or innovation in medical treatment [1]. Approximately 60% of patients with chronic disease have less than optimal levels of adherence [2]. In 2018, the annual costs of medication non-adherence was estimated to be approximately $290 billion in the USA, €25 billion in Europe and $7 billion in Australia [3]. Given fiscal restraints within health care systems, it is prudent to understand the factors that contribute to low levels of adherence in patients with chronic disease. Coupling this information with a theoretical foundation can then allow for research into interventions to improve adherence [4].

Haemophilia is a chronic disease in which blood cannot clot due to the absence or deficiency of a clotting factor protein. The two most common types are haemophilia A (Factor VIII deficiency) and haemophilia B (Factor IX deficiency) [5]. Haemophilia has an estimated frequency of one per 10,000 births and there are approximately 400,000 people with haemophilia worldwide [5]. For both haemophilia A and B, joint bleeding accounts for 70% to 80% of all bleeding episodes [5]. Although any joint may be affected, hinge joints, particularly the ankles, knees and elbows, are the most commonly involved [5]. Treatment for haemophilia involves the intravenous replacement of the missing clotting factor using various treatment regimens. Prophylaxis, also known as regular replacement therapy, is treatment given continuously for 52 weeks per year to prevent or reduce the risk of bleeding [6,7]. On-demand treatment is when factor is given in response to a bleeding episode. In comparison to on-demand treatment, prophylaxis offers greater protection from life-threatening haemorrhages, prevention of joint bleeding, lower annualised bleed rates, and improved quality of life [7]. Dosage and frequency of prophylaxis infusions is determined by a number of factors including, bleeding phenotype, venous access, goals of treatment, age of the patient, and the costs of treatment [7]. With the recent advances in extended half-life factor products and the ability to provide individualised prophylaxis recommendations through population pharmacokinetic modelling, prophylaxis recommendations are also being guided by minimum trough levels. Currently, the goal for many developed countries is a minimum trough level of 1–5% to prevent breakthrough bleeding [7]. Given the required frequency of infusions to achieve the goals of prophylaxis, and to ensure prompt access to treatment in the event of a bleed, patients/caregivers are trained to perform factor infusions at home.

While home infusion offers many benefits, adherence to prophylaxis recommendations is variable [8], potentially leading to recurrent joint and muscle bleeding [9]. Joint disease affects 90% of people with severe haemophilia and contributes the greatest cost and morbidity in the haemophilia population [10]. Prophylaxis improves joint outcomes by decreasing the number of bleeding episodes and preventing the development of chronic arthropathy [11]. Effectiveness of prophylaxis is influenced by dosage and frequency but more importantly by patients adhering to factor treatment recommendations [11]. Adherence to treatment recommendations is a complex phenomenon influenced by personal and societal variables. In patients with haemophilia, reported levels of adherence ranges from 17–82% [12-14]. Reasons for the large variation in levels of adherence include both measurement and treatment-related issues.

Measurement-related issues include a lack of accepted definition of adherence and the different measures used to calculate adherence, while treatment-related issues may include the time-consuming nature of prophylaxis treatment, the cost of factor therapy, the perceived lack of benefit, frequent venous access, lifestyle disruptions, cooperation of the patient, and the complexity and duration of treatment [12-14]. Given the number of variables and wide range of adherence, further research is needed to understand the relationship between adherence and clinical outcomes [12]. Crucial to this process is the systematic evaluation of the predictors of treatment adherence using theoretical models as a foundation [15].

Investigation into the predictors of treatment adherence in chronic diseases, such as haemophilia, should start with a consideration of relevant theory, in order to provide a structure to generate hypotheses, and to conceptualise ideas to organise, predict and explain certain events or behaviours [4]. Ecological theory takes into account the influence of different levels of the health care system on patient behaviour [16]. The WHO Multidimensional Adherence Model (MAM) is an ecological model that combines intrapersonal, interpersonal, organisational, policy, and community barriers, to understand adherence behaviour [15,16]. The MAM framework classifies barriers to adherence into five dimensions: health care team/health system, socioeconomic factors, patient-related factors, condition-related factors and treatment-related factors (see Figure 1) [15,16]. The MAM also highlights the need for a multidisciplinary approach to adherence, which fits well within the comprehensive model of care that has been adopted in the treatment of haemophilia in Canada [17].

This study is the first to investigate treatment adherence in patients with haemophilia using the MAM. The primary purpose was to determine which combination of factors (infusion frequency, annualised bleed rate, age, distance to the haemophilia treatment centre (HTC), Haemophilia Joint Health Score (HJHS)) best predicts adherence to treatment recommendations in patients with haemophilia A and B on home infusion prophylaxis in Canada using two measures of adherence. The secondary purpose was to determine which of the two measures of adherence produced the most explanatory model.

METHODS

Study design
This was a one-year retrospective cohort study.

Data sources
Data were extracted from the medical record and the Canadian Bleeding Disorders Registry (CBDR). The CBDR is a collaboration among the Association of Hemophilia Clinic Directors of Canada (AHCDC), McMaster University and the Australian National Blood Authority, with support from the Canadian Hemophilia Society. The CBDR is a national registry and clinical database for patients with bleeding disorders, and is used by HTCs to support patient care, improve research and monitor factor concentrate utilisation [18]. The CBDR is linked to MyCBDR, a web-based home

Figure 1: World Health Organization Multidimensional Adherence Model [15]
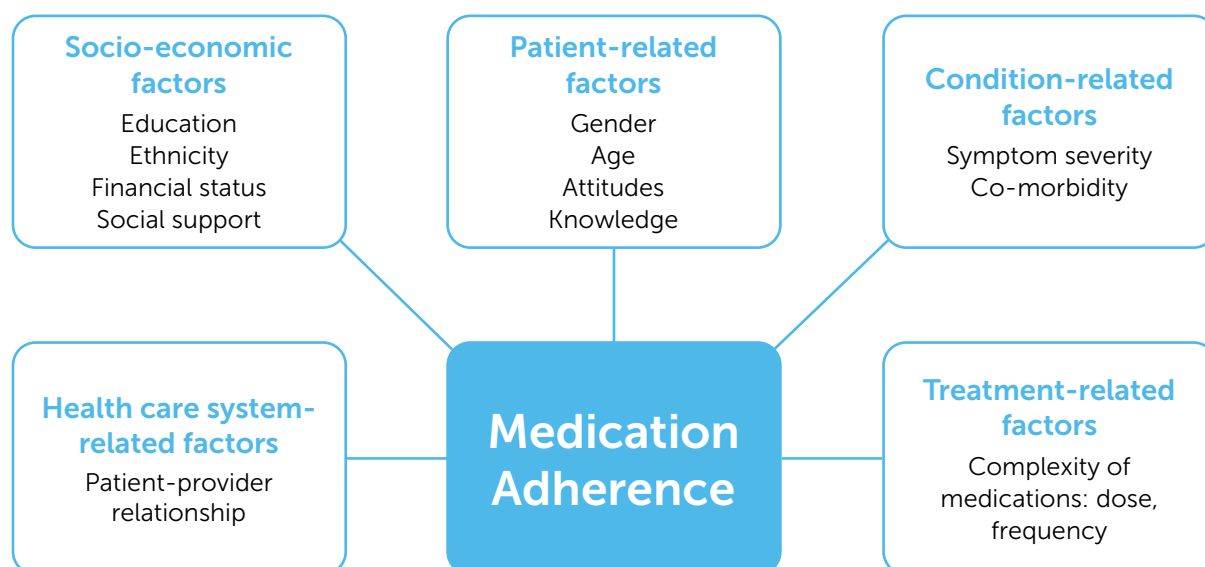
infusion patient diary. The AHCDC owns the CBDR and MyCBDR; McMaster University manages the system on behalf of the AHCDC and regularly performs data cleaning initiatives to ensure fidelity of the data.

Setting
The HTC Comprehensive Care Model (CCM) is the standard of care for haemophilia in Canada. The CCM focuses on family-centred care and the prevention of the acute and chronic manifestations of a bleeding disorder through education and coordination of services available within the HTC and the surrounding region [19]. For this study, data were accessed for patients from a large urban HTC in Canada.

Study procedures
Retrospective data were extracted and anonymised from the CBDR, MyCBDR and the medical record for the 2017 calendar year. Ethics approval was obtained from the Hamilton Integrated Research Ethics Board.

Participants
All patients with haemophilia A or B who were prescribed prophylaxis via home infusion were included. Patients receiving prophylaxis in long-term care, via community resources and those in research studies were excluded.

Sample size
Although sample size formulae exist with respect to evaluating the entire model (e.g., is the R-squared different from a null value) and whether the addition of one or more variables (the number being specified by the investigator a priori) add to its predictive ability given the presence of covariates, there is no accepted formula for sample size for stepwise regression. An important consideration with stepwise regression is the number of 'behind the scenes' multiple comparisons and phantom degrees of freedom applied to come up with the final model [20]. This has the potential, based on chance, to include variables that are truly not predictive of outcome, as well as to miss variables that are truly predictive of outcome. Accordingly, the stability of a given model is determined by cross-validation and the calculation of shrinkage. Therefore, a convenience sample of all eligible subjects was used and an acceptable level of shrinkage was set at 10% or less [21].

Variables
Dependent variable: treatment adherence
There is currently no gold standard for the evaluation of medication adherence [1]. In clinical research, adherence

is often measured by the number of doses used by the patient compared to the number of doses prescribed by the physician [7]. In this study, two measures of adherence that are readily available in the CBDR were used. The first, a subjective report, was calculated as a percentage of reported factor usage via home infusion diaries divided by the physician prescribed dose for the 2017 calendar year. The second, an objective report, was calculated as a percentage of factor inventory ordered by the patient via the Canadian Blood Services divided by the physician prescribed dose for the 2017 calendar year. The subjective report assumed that if there was no record, then the infusion was not given. The objective report assumed that all factor ordered for home infusion was for prophylaxis and was used as prescribed. For both measures, the physician prescribed dose was for prophylaxis treatment recommendations. Given these assumptions, both methods were used to determine which method resulted in the most explanatory model.

Explanatory variables
The candidate variables were chosen to align with the MAM.

Distance from home (health care system-related factors)
Health care system-related factors include systems, organisations or access to health care professionals who provide care to patients [17,22]. The amount of time spent within the HTC and the relationship with the team is strongly associated with adherence [23]. Access to the HTC, as measured by the distance in kilometres (km) from the patient's home address recorded in the CBDR to the address of the HTC, was calculated and investigated as a health care system-related factor. For this study, it was hypothesised that burden of travel to the HTC would limit time spent in the HTC. It has been shown in the literature that for patients with chronic disease, transportation is essential for ongoing health care and access to treatment and medication [24]. Burden of travel has been defined by the US Department of Transportation as travelling greater than 30 minutes or 30 miles/48 km to a health care provider [24].

Age (socioeconomic and patient-related factors)
Socioeconomic factors relate to social and economic status [17,22]. Patient-related factors can include patient characteristics such as sex, age, attitudes and beliefs [17,22]. In the current study, age is used to represent both domains. Age can represent the availability of social supports as paediatric patients have family/caregivers trained to assist with home infusions while adult patients

perform self-infusion. Adolescence and the transition to adult care is a particularly important timeframe as this period is often associated with increased independence in disease management with the transfer of responsibilities from the caregiver to the patient [25]. Adolescence is also a time of personal change, which may impact adherence to prophylaxis treatment [25]. During this transition, it has been found that 41% of patients with haemophilia aged 13–25 years did not follow the prescribed treatment recommendations [26]. In a study of nurse-reported data, Geraghty et al. found levels of adherence of 90% in patients aged 0–12 years, 54% in patients aged 13–18, and 36% in patients aged 19–28 years [27]. A Canadian survey suggests that paediatric patients have higher levels of adherence than adolescents or adults [28,29]. Increasing age is also associated with lower levels of adherence [23]. Age was calculated in years as of January 1, 2017.

Annualised bleed rate and HJHS (condition-related factors)

Condition-related factors are characteristics such as symptom severity and comorbidity [17,22]. Symptoms, such as bleeding episodes and pain from chronic arthropathy, have been shown to be both a positive and negative motivator for adherence in haemophilia [23,30]. The study used the annualised bleed rate (ABR), or number of bleeds over one year, as a measure of disease activity. ABR is a patient-reported measure and potentially limited by patients' failure to accurately report a painful episode, subclinical bleeding and social desirability [31]. However, ABR is still a widely used outcome of treatment efficacy in the majority of clinical trials in haemophilia. Typically, patients on prophylaxis will have a mean ABR of 3.27 [32].

Joint disease, once established, is progressive and irreversible [33]. Poor adherence to treatment recommendations is associated with worse joint outcomes [32] and greater symptom severity. The Haemophilia Joint Health Score (HJHS) is an objective measure of joint health in patients with haemophilia [34-37]. Scores range from 0–124 with higher scores indicating worse joint disease [34,35]. The HJHS demonstrates acceptable psychometric properties in paediatrics including excellent test-rest (ICC=0.89) inter-observer (ICC=0.83) reliability, and internal consistency (Cronbach's alpha=0.86) [35]. With regard to construct validity, the HJHS shows good ability to discriminate between known groups of patients and it correlates appropriately with bleeding rates (rs=0.50) and physician global assessment of joint health

(rs=0.42) [34, 36]. Criterion validity has been demonstrated and the HJHS correlates well with radiographic changes and favourably with the World Federation of Hemophilia Physical Examination Score when discriminating known groups (63–97% more efficient) [34,36,37]. A validation study in adults is currently underway (N. Zourikian, co-developer of the HJHS, oral communication, May 2019). For this study, one HJHS score for the 2017 calendar year was extracted from the CBDR. In the event that two scores were completed, the higher score was used.

Infusion frequency (treatment-related factors)

Treatment-related factors are associated with treatments or influence a patient's willingness to receive treatment [17,22]. The time required for prophylaxis has been considered a significant barrier to treatment adherence [32]. Infusion frequency typically ranges from once per week to daily. For this study, infusion frequency was assessed categorically with the following groupings: 1 = one infusion/week; 2 = two infusions/week; 3 = three infusions/week; 4 = infusions every other day; 5 = infusion every three days; 6 = infusion every five days; 7= daily infusions.

Analyses

Statistical analyses were conducted with alpha set at 0.05 using Stata v.14. Descriptive statistics were reported as means, standard deviations, 95% confidence intervals (CI) for continuous variables given a normal distribution and as medians, quartiles for skewed distributions. Counts and percentages were applied to categorical data. Normality was assessed with the Shapiro Wilk test/histogram. Correlation graph matrix and correlation coefficients were investigated to assess for collinearity and the relationship of the explanatory variables with both measures of adherence. If collinearity was found, one of the explanatory variables was removed. Homoscedasticity was assessed with the Breusch-Pagan test. For the subjective measure, the assumption of normality could not be met and a stepwise regression analysis that applied robust standard errors was completed.

To achieve normality, the objective measure was raised to a power of two and a stepwise regression was performed with 0.05 level of significance for model entry and 0.10 for model removal. Regression diagnostics were performed, and outliers were considered for removal from the data set based on clinical plausibility and influence. Normality of residuals was assessed by the Shapiro-Wilk test/histogram, homoscedasticity via the Breusch-Pagan test and multicollinearity via variance inflation factors. Validation of the final model was

completed using resampling validation, bootstrapping with 200 samples and shrinkage analysis.

The final response variable variation (R2) and regression diagnostics could determine which measure of adherence results in the most explanatory model. Combining this information with relevant clinical theory and logic, would allow for the selection of the preferred measure of adherence.

RESULTS

Eighty-seven patients met the inclusion criteria. The median age was 21 years (1st and 3rd quartiles: 10, 36) and consisted largely of patients prescribed a prophylaxis regimen of every other day (34%). The median, 1st and 3rd quartiles for the subjective measure of adherence was 81% (51, 98). The mean, standard deviation for the objective measure of adherence was 93.55% (24.75). Median scores on the HJHS was 10.5, ABR was two and distance to the HTC was 51km. Descriptive statistics are presented in Table 1. As there was a high correlation between HJHS and age (r2= 0.86), HJHS was removed from both analyses. The correlation matrix is presented in Table 2.

Table 1. Characteristics of outcome and explanatory variables

VARIABLE	N	MEAN/SD	MIN/MAX (%)
Objective measure of adherence†	87	93.55/24.75	0/154%
	N	MEDIAN	1ST & 3RD QUARTILES
Subjective measure of adherence‡	87	81	51, 98
ABR§	87	2	0, 4
Age¶	87	21	10, 36
Distance from HTC††	87	51	26, 71
HJHS‡‡	76	10.5	1, 23.5
	CATEGORIES	COUNTS	PERCENTAGE OF SAMPLE
Infusion frequency§§	1	8	9%
	2	20	23%
	3	21	24%
	4	30	34%
	5	2	2%
	6	1	1%
	7	5	6%

Table 2. Correlation matrix
Correlation co-efficient of the explanatory variables with both measures of adherence

	SUBJECTIVE	OBJECTIVE	HJHS	AGE	FREQUENCY	ABR	DISTANCE
Subjective‡	1.0000						
Objective†	0.4568	1.0000					
HJHS‡‡	-0.0228	0.0651	1.0000				
Age¶	0.0128	0.0375	0.8573	1.0000			
Frequency§§	0.0402	-0.1959	-0.0250	-0.0351	1.0000		
ABR§	-0.0861	0.0310	0.3438	0.2597	-0.0236	1.0000	
Distance††	0.0977	-0.0307	0.0442	0.0690	-0.0346	0.2038	1.0000

Key to Tables 1 and 2
† Objective measure of adherence: percentage of factor inventory ordered by the patient via the Canadian Blood Services divided by the physician prescribed dose
‡ Subjective measure of adherence: percentage of reported factor usage via home infusion diaries divided by the physician prescribed dose
§ ABR: annualised bleed rate = number of bleeds a patient experiences over one year
¶ Age: in years as of January 1, 2017
†† Distance from HTC: distance in kilometres (km) from the patients' home to the haemophilia treatment centre.
‡‡ HJHS: Haemophilia Joint Health Score version 2.1.
§§ Infusion frequency with the following legend: 1 = one infusion per week; 2 = two infusions per week; 3 = three infusions per week; 4 =infusions every other day; 5 = infusion every three days; 6 = infusion every five days; 7= daily infusions.

Table 3. Full model stepwise regression for the objective measure of adherence

VARIABLE	β-COEFFICIENT	STD ERROR	P-VALUE	95%CI
Frequency	-672.394	324.506	0.041	-1317.599, -27.189
_cons†	11536.88	1147.566	0.000	9255.207, 13818.54

†_cons = represents the constant or intercept for the regression line

Stepwise regression for the objective measure of adherence

Initial residual analysis showed skewing of the objective adherence measure which was corrected by squaring the dependent variable. Stepwise analysis revealed that age, distance to the HTC and ABR were not statistically significant, leaving infusion frequency (p=0.041) in the final model with an R^2 of 0.048, adjusted R^2 of 0.037 (Table 3). However, the shrinkage was 83%, indicating a lack of stability.

Stepwise regression for the subjective measure of adherence

There was severe skewing of the subjective adherence measure with a preponderance of observations showing extremely high adherence. Several transformations were attempted; however, these were unsuccessful. Accordingly, a stepwise regression with robust standard errors was performed. None of the variables were predictive of subjective adherence (R^2=0).

DISCUSSION

Adherence is a multifaceted construct and is influenced by many factors. Use of the MAM to conceptualise and select explanatory variables to predict adherence is a strength of this study. Analysis of the objective measure weakly supported the relationship of infusion frequency as a treatment-related factor for adherence. Less frequent infusion regimens are associated with improved adherence for both patients with chronic disease in general and in patients with osteoporosis [38]. For patients with haemophilia, with the availability of extended half-life products and the possibility of less frequent infusions, patients may become more adherent [32,38]. While higher infusion frequencies were associated with lower levels of adherence in this study, infusion frequency explained only 4.8% of the variance and is not considered clinically relevant. Closely related to infusion frequency is venous access. As factor replacement therapy must be given intravenously, venous access has been shown to be a potential barrier to adherence [14,23]. As this study found, a weak association with adherence and infusion frequency, future studies should include methods of venous access as a potential predictor of adherence.

There is no gold standard for the measurement of adherence in patients with haemophilia [39]. Various methods of measuring adherence have been reported in previous studies, including patient surveys, physician/nurses perception of adherence ratings, interviews, analysis of infusion diaries, and self-reported questionnaires such as the VERITAS-Pro [28,38-41]. However, none of these measures have been validated for patients with haemophilia in Canada, and the heterogeneity in measurement presents barriers to the analysis of predictors of adherence and are important directions for future research.

This study investigated two measures of adherence using data that is readily available in the medical record, the CBDR and home infusion diaries. However, due to the complexity of the adherence construct and the lack of clinical relevance of either model, we were unable to determine which measure provided the most explanatory model. Combining patients with both haemophilia A and B in the sample may affect the generalisability of the results, as patients with haemophilia A have treatment recommendations with a greater frequency of infusions. Further, adherence to prophylaxis over the lifespan further complicates the relationship [42,43]. Predictors may be interdependent and there may be commonalities and differences among groups of patients with different levels of adherence. Future analyses using hierarchical regression with patient clustering by adherence, age or diagnosis could provide further insight.

The results indicate that there are other predictors of adherence in patients with haemophilia. Although the MAM aims to be an inclusive model of adherence, this study demonstrates that system-level factors are potentially less predictive of adherence than assumed within a well-organised socialised healthcare system such as that found in Canada. Due to the availability of system-level data in the medical record and the CBDR, the variables used to investigate adherence focused on clinical and demographic factors with a lack of patient-related variables. Research on adherence in patients with heart failure using the MAM found that the most important and consistent predictor of poor adherence was patient perception of the barriers to adherence,

such as forgetting medication and the belief that missing a dose will not be harmful [15]. Condition-related factors (i.e. patient function), and socioeconomic factors (i.e. social supports, ethnicity, financial status) were related to at least one indicator of adherence [15]. Currently, there is a lack of data on patient perceived barriers to adherence and socioeconomic factors for patients with haemophilia and their families available in the CBDR, and given the lack of variance explained by system level factors, this is a limitation of the current study. A prospective study with the inclusion of the patient's perspective, patient function and socioeconomic factors is an important consideration for future research.

Although, patients in this study demonstrated high levels of adherence, there was a wide range with a minimum/maximum of 0−154% reported. The high level of adherence in this sample may be due to clinic policy to reduce the amount of factor per order until home infusion records are received. Further, staff demonstrate how home infusion records assist in clinical decision making by engaging patients in the analysis of bleeding episodes. Patient engagement and individualised treatment recommendations improve adherence [32]. Within the HTC, individualisation of care has expanded to include pharmacokinetics with the Web Accessible Population Pharmacokinetic Service [44]. Non-adherence in this study was characterised by missed infusions or a lack of ordering sufficient amounts of factor to fulfil prophylaxis recommendations. Bleeding events, over-administration of factor resulting in an adherence rate of greater than 100%, and timing of infusions were not investigated, all of which may have decreased the ability to detect differences in adherence. Future studies that use the amount of factor dispensed as an estimate of adherence should consider using methods that adjust for bleed reporting [31].

Despite previous research demonstrating adolescence [29], increasing age and lack of experience of symptoms as significant barriers to adherence [23], no relationship was found in this study. Seventy-five per cent of the sample was under 36 years of age and the median age was 21 years. The disproportionate number of zero scores on the HJHS (22%, age range 1−13 years) and the median score of 10.5, makes interpreting the HJHS difficult. The significant collinearity with age and HJHS further influenced the analysis, as it is well known that joint health deteriorates with age. Consistent with the expectation of three bleeds per year in patients prescribed

prophylaxis [32], this sample of patients demonstrated a median ABR of two. Therefore, this sample included patients who were younger with minimal joint arthropathy and limited experience of symptoms, which may impact generalisability as the sample may not represent the broader haemophilia population in Canada. Although all eligible patients and data were included in this study, the convenience sample may not be adequately powered and is a possible limitation. Future research with a larger, more heterogeneous population is warranted.

CONCLUSION

Adherence to prophylaxis is the most effective method of preventing or delaying the development of arthropathy and functional decline in patients with haemophilia [32]. This is the first study to investigate the predictors of treatment adherence in patients with haemophilia A or B on prophylaxis using the MAM. In spite of a theoretical approach, a strong methodological and conceptual rationale for the selection of explanatory variables, and the use of two measures of adherence, there were no clinically relevant findings and most of the variance in adherence in this sample remains unknown. Infusion frequency is a possible predictor of adherence that requires further study. It appears that there are other potential predictors of adherence and further research on the possible variables and relationships within factors of the MAM is required.

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