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A tailored intervention for illness acceptance improves adherence and quality of life in adults with haemophilia using prophylaxis

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Abstract

Introduction: Adherence to prophylactic treatment (prophylaxis) in persons with haemophilia is challenging and has been reported at only ±50%. Acceptance problems are one of the main reasons for non-adherence in haemophilia. An evidence-based intervention was developed based on an acceptance and commitment therapy (ACT) approach.

Aim: To evaluate a tailored intervention focused on illness acceptance in adults with haemophilia who were prescribed prophylaxis.

Methods: A pre-post study was executed in adults with haemophilia who were prescribed prophylaxis. A series of 8 2-hour group trainings were held, including 3-8 participants/series. Adherence (VERITAS-Pro, optimum 0), health-related quality of life (HRQoL, SF-36, optimum 100) and illness perception (BIPQ, optimum 0) were measured at start, after six months and 12 months and analysed using Wilcoxon signed-rank test.

Results: Twenty-four patients (median age 47 years, range 27-74) were included. After 12 months, adherence improved in 68% of patients, quality of life in 48% and illness perception in 31%. Adherence (total score) improved from 35 to 25 ($P<0.01$). HRQoL showed clinically relevant improvement in domains of social-functioning ($P = 0.04$), role-emotional, physical-functioning, role-physical and bodily pain. Illness perception improved statistically significant on domains of affect ($P = 0.01$), concern ($P = 0.01$) and understanding ($P = 0.04$). Patients evaluated the training useful, an eye-opener, a personal enrichment and insightful.

Conclusion: The tailored group intervention resulted in significant improvement of adherence, quality of life and illness perception. Based on our current experience, we have implemented it in clinical practice and collaborate with the patient association to make it available for all Dutch people with haemophilia.

KEYWORDS
adherence, haemophilia, illness acceptance, intervention, quality of life

1 | INTRODUCTION

Haemophilia is a rare bleeding disorder, affecting approximately 1700 Dutch men, including ±800 with severe haemophilia.[1] Patients with severe haemophilia have no measurable clotting factor FVIII or FIX and are at risk for spontaneous bleeds in joints, muscles or the central nervous system.[2] Treatment consists of lifelong prophylactic clotting factor replacement therapy (prophylaxis).[1,3] Patients using prophylaxis perform intravenous injections at their homes approximately 2-3 times a week.[2,3]

For effective prevention of bleeding, high adherence to the prescribed treatment is crucial. Similar to other chronic conditions, the non-adherence rate in haemophilia is estimated at 50%.[4] Non-adherence is very harmful, as even a single bleed can lead to irreversible damage with potential lifelong disabilities.[5] Previous research identified acceptance problems (present in ±25% of patients) as one of the main reasons for non-adherence.[6,7] Patients with acceptance problems mostly administer concentrate inadequately (eg only to treat bleeds, or dosing once weekly) and are thus at risk for serious bleeding.[6]

Acceptance and commitment therapy (ACT) is a proven effective approach to support patients with illness-related acceptance problems.[8-11] ACT is a psychological intervention combining acceptance, mindfulness, cognitive and behavioural therapy. This theory is focussed on changing a person's thoughts resulting in habit changes.[12] This method has been used in many diseases (eg HIV, cancer, epilepsy) with positive results like improving quality of life and symptom control and reducing distress.[13]

Based on ACT, a tailored group invention for patients with haemophilia on prophylaxis was developed.[14] The intervention focused on illness acceptance showed promising results during feasibility testing.[14] This study aimed to evaluate the effect of the tailored invention for patients with haemophilia who were prescribed prophylactic treatment.

2 | MATERIALS AND METHODS

A prospective pre-post-test study evaluated the effectiveness of a tailored intervention called 'living with haemophilia' (in Dutch 'Leven met hemofilie'). This training was based on the already existing and proven effective 'Acceptance and Commitment Therapy' (ACT).[9,11,13] The study design is shown in Figure 1. Patients completed a questionnaire prior to the intervention, followed the group training and subsequently completed questionnaires at six and twelve months after the first training session. The study was approved by the ethical committee of the University Medical Center Utrecht, the Netherlands.

2.1 | Participants

Adult patients (>18 years) from all treatment centres of the Netherlands were eligible to participate if they were diagnosed with haemophilia and when prophylactic treatment was prescribed or indicated.
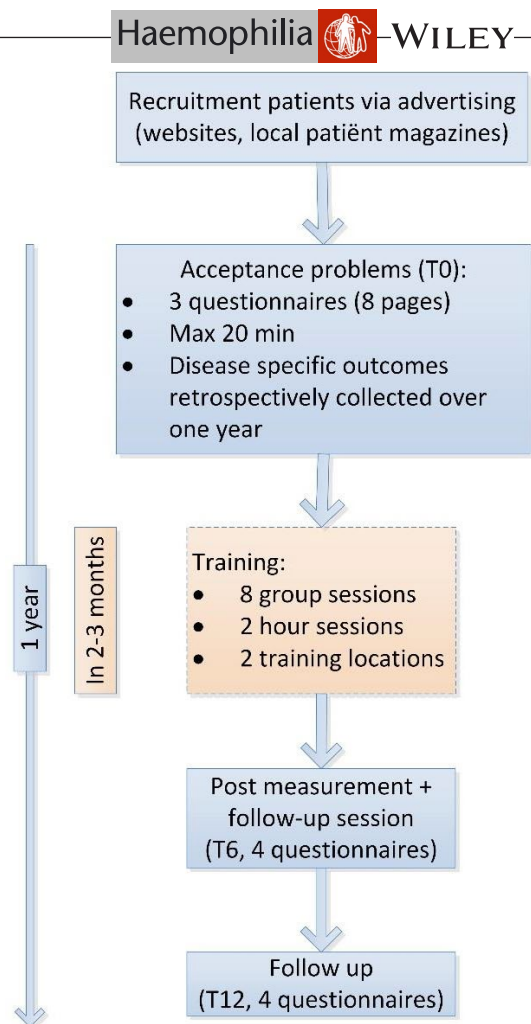

FIGURE 1 Study design

Patients were excluded when they were diagnosed with a serious psychiatric disorder, which could potentially interfere with the training.

Patients were informed about this study by their healthcare provider or through different digital platforms (websites, social media, newsletters and the patient society). When a patient was considering participation, a phone call with one of the trainers (RB, LH or JH) was scheduled to inform the patient and clarify his personal training goal. Patients signed informed consent prior start of the training. A formal power calculation was impossible due to lack of information and the small population. Prior to the study, the team considered 23-32 participants sufficient to evaluate outcome.

2.2 | Data collection

Data were collected before start, after six months and after twelve months. The primary outcome was adherence,[15,16] and secondary outcomes were health-related quality of life,[17] illness perception[18] and disease-specific outcomes. Adherence was assessed according to two quantitative methods: firstly based on the Delphi definition of non-adherence[15] evaluating missed infusions, dose changes and deviation in timing and secondly using the Validated Hemophilia Regimen

Treatment Adherence Scale—Prophylaxis (VERITAS-Pro). The VERITAS-Pro consists of 24 questions resulting in a total score and six domain scores (time, dose, plan, skip and communicate). An increase of 5 points on the total score was considered of clinical relevance. VERITAS-Pro scores were normalized (0 indicates perfect adherence). Quality of life (QoL) was measured using the short form 36 health survey (SF-36) (100 indicates perfect QoL).[17] The SF-36 consists of 36 questions in 8 domains, which can be subdivided into mental components including vitality (V), social functioning (SF), role-emotional (RE) and mental health (MH) and physical components including the domain physical functioning (PH), role-physical (RH), bodily pain (BP) and general health (GH). An increase of 5 points is considered clinically relevant.[19] Disease perception was measured using the Brief Illness Perception Questionnaire (BIPQ).[20] The BIPQ consists of eight stand-alone questions, scoring from 0 to 10[21] (0 indicates perfect illness perception). A higher score represents a more threatening view of the illness. Because haemophilia is a lifelong disease, we decided to remove the second question (Q2. How long do you think your illness will continue?). Clinical relevance was considered when a patient increased with 2-3 points (25th percentile). During the last session, the training was evaluated using a qualitative group interview. This interview was executed by the trainers and was recorded.

2.3 | Data analysis

Missing data by not completing a questionnaire were not replaced. In case of missing data by conscious skipping specific questions (on-demand regime instead of prophylactic regime), data were replaced (adherence cut-off value). Patient characteristics were analysed using descriptive statistics and reported as medians and interquartile ranges (IQR). Changes from start to 12 months of follow-up at patient level were analysed using descriptive statistics. Data originating from questionnaires were presented as means and standard deviations (SD).[22] The VERITAS-Pro was normalized into a 0-100 score (score-24/96*100, optimum 0 points). Differences over time were analysed using the Wilcoxon signed-rank test. Qualitative evaluation was summarized and analysed according to themes identified. The research team discussed the themes.

3 | RESULTS

In total, 24 of 80 invited patients (response rate: 30%) signed informed consent and participated in the training. All patients completed the training and the majority of the patients completed the questionnaires (90%, 69/72 questionnaires) at the appropriate time.

3.1 | Patient characteristics

Patient characteristics are shown in Table 1. The majority of the patients was diagnosed with haemophilia A (N = 23, 96%) with a severe

TABLE 1 Patient characteristics

	Participants	
	N = 24	% or IQR
Haemophilia A	23	(96%)
Severe	22	(92%)
Moderate	1	
Age (y)	47	(39-56)
Prescribed frequency per week (med/IQR)[a]	3	(3-3)
Prescribed FVIII dose/infusion (med/IQR)[a]	1000	(750-1625)
Education level		
Primary education	1	(4%)
High school	4	(77%)
Vocational education	8	(33%)
Advanced vocational	7	(29%)
University	4	(17%)
Employment		
Full-time paid	14	(58%)
Part time	2	(8%)
Unable to work	6	(25%)
Other	2	(8%)
Absence due to bleeds (IQR)	0	(0-2)

[a]Haemophilia A only.

(N = 22, 92%) phenotype. The median age was 47 years (IQR: 39-56, range 27-74). The median prescribed frequency of prophylactic injections was three times a week (IQR: 3-4) with a prescribed dose of median 1000 units per infusion (IQR: 750-1625). The majority of patients completed vocational education (N=8, 33%) and were full-time employed (N = 14, 58%).

3.2 | Adherence

Adherence increased (+ ≥5%) in 68% of the patients. Adherence over time is shown in Table 2 and Figure 2. Based to the Delphi definition of non-adherence, an improvement on all three domains was observed. Two improved significantly after six months: domain 'administer prophylaxis' (increase by 14% $P = 0.04$) and domain 'correct time' (increase by 17%, $P = 0.01$). One domain was still significantly improved after 12 months: 'correct time' (increase by 19%, $P = 0.01$). Based on the VERITAS-Pro, an improvement (ie lower score) on the total score and all six domains was observed. Two domains improved significantly after 6 months: domain 'time' (−14 points, $P = 0.03$) and domain 'remember' (−10 points, $P = <0.04$). After 12 months, the total score and four domains significantly improved: 'Total score' (−10 points, $P = <0.01$), domain 'time' (−18 points, $P = 0.02$), domain 'remember' (−12 points, $P = 0.03$), domain 'skip' (−13 points, $P = 0.02$) and 'communicate' (−26 points, $P = 0.04$).

TABLE 2 Adherence measured with the VERITAS-Pro (normalized values 0-100, optimum 0)

| Number	T0	T6	T6-T0	P value[a]	T12	T12-T0	P value[a]
	24	22	22		23	23	
	Mean (SD)				Mean (SD)		
Total score	35 (13)	30 (13)	−5	0.14	25 (12)	−10	**<0.01**
Time	42 (27)	28 (23)	−14	**0.03**	24 (18)	−18	**0.02**
Dose	18 (15)	22 (18)	+4	0.46	13 (9)	−5	0.10
Plan	34 (20)	32 (24)	−2	0.76	32 (20)	−2	0.34
Remember	42 (22)	32 (26)	−10	**0.04**	30 (21)	−12	**0.03**
Skip	37 (24)	28 (22)	−9	0.09	25 (21)	−12	**0.02**
Communicate	52 (17)	36 (17)	−16	0.65	26 (16)	−26	**0.04**

[a]Wilcoxon signed-rank test.

FIGURE 2 Adherence over time
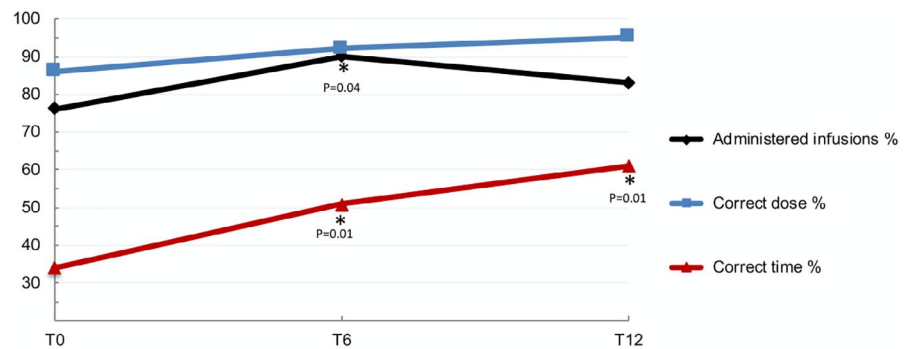
* Indicates a significant (P=≤0.05) difference relative to baseline. Wilcoxon signed rank test was used.

FIGURE 3 Health-related quality of life
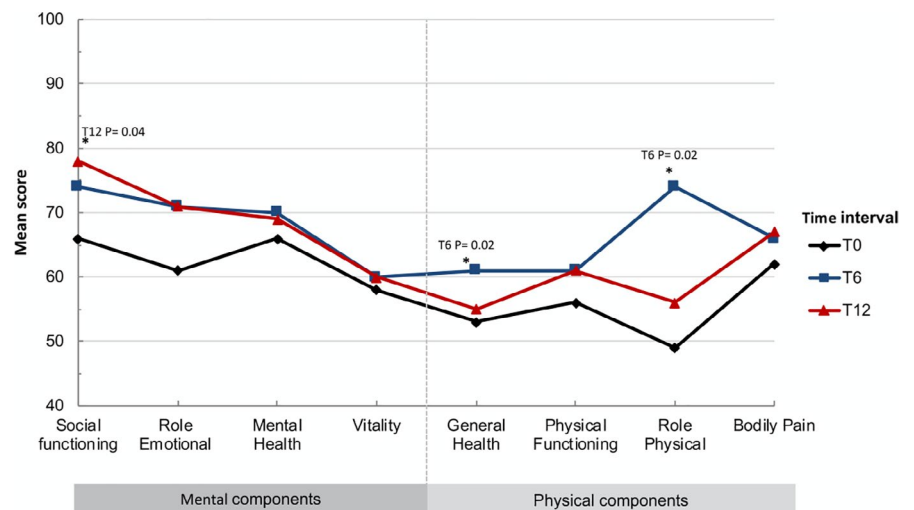
* Indicates a significant (P=≤0.05) difference relative to baseline. Wilcoxon signed rank test was used.

3.3 | Health-related quality of life

Health-related quality of life improved (+ ≥5 points) in 30–48% of the patients (depending on the different domains). HRQoL over time is shown in Figure 3. HRQoL improved on all domains. After six months, 5/8 domains showed clinically relevant improvement: 'social functioning' (+ 8 points), 'role-emotional' (+ 10 points), 'physical functioning' (+ 5 points), 'role-physical' (+ 25 points, P = 0.02) and 'general health' (+ 8 points, P = 0.02). After 12 months, HRQOL scores were again compared to T0. 'Social functioning' improved further to eventually +12 points (P = 0.04), while 'role-emotional' (+10 points) and 'physical functioning' (+ 5 points) remained stable since six months of measurement moment. Compared to the measurement moment (+25 points), the improvement in the domain of 'role-physical' was partly reversed to end at +7 points and the domain of 'bodily pain' had increased by 5 points.

3.4 | Illness perception

Illness perception increased in 31–68% of the patients (depending on the specific question). Illness perception (BIPQ) scores according to time are shown in Table 3. Based on the BIPQ, at six months two questions showed statistically significant improvement: 'illness related concerns' (improved in 59% of the patients, $P = 0.04$) and 'illness affected emotions' (improved in 59%, $P = 0.00$).

After twelve months, statistically significant improvement remained in 'illness related concerns' (improved in 56%, $P = 0.01$), while 'illness affected emotions' showed no improvement compared to start. In addition, statistically significant improvement was observed for 'illness affecting life' (improved in 65%, $P = 0.01$) and understanding illness (improvement in 57%, $P = 0.04$).

3.5 | Qualitative evaluation

Participants evaluated the training as useful, an eye-opener, a personal enrichment and insightful:

R11: 'This training met my expectations, exceptionally good'.
R14: 'It was more fun than I expected.'

Participants appreciated the peer contact and stressed the importance of sharing experiences. In addition, they appreciated that this training was more than just 'talking'. The exercises were considered valuable:

R10: 'I experienced the combination of sharing experiences and exercises related to difficulties someone is facing as very powerful'.

One participant mentioned that he would have liked to have more sessions to create more time for reflection. None of the participants experienced eight sessions as too many. They appreciated the added value of peer contact compared to individual sessions with a psychologist. All participants recommend the training to others.

R21: 'The conversations and questions are challenging me. The training really changed my mind and thoughts. That is what I liked about this training and why I would like to recommend it to others'.

4 | DISCUSSION

This study aimed to evaluate the effect of a tailored intervention focused on illness acceptance for patients with haemophilia on prophylaxis. The training was evaluated as effective, clinically relevant improvement in adherence was observed in 68% of patients, health-related quality of life improved in 48%, and illness perception improved in 31 of patients. Adherence improved significantly on the VERITAS-Pro domains of 'time', 'remember', 'skip' and 'communicate'. Quality of life improved on both mental components and physical components, with statistically significant improvement in the domain of 'social functioning'. In addition, Illness perception improved significantly on 'illness affecting life', 'related concerns' and 'illness understanding'. Patients evaluated the training positively, completion was 100%.

4.1 | Strengths and weaknesses

Consistency and quality of the training was maintained by formally trained trainers, a fully scripted training and hands-on training for all trainers (ACT-certified).[14] The training was executed by haemophilia

TABLE 3 Illness perception (range 0-10, optimum 0)

Number	T0 24 Mean (SD)	T6 22 Mean (SD)	Improvement	T12 23 Mean (SD)	Improvement
Q1 How much does your illness **affect** your life?	7 (2)	6 (2)	68%	6 (2)	65%[a]
Q3 How much **control** do you feel you have over your illness?	3 (2)	6 (2)	36%	3 (2)	39%
Q4 How much do you think your **treatment** can help your illness?	3 (2)	2 (1)	36%	1 (2)	48%
Q5 How much do you experience **symptoms** from your illness?	7 (2)	7 (2)	31%	7 (2)	43%
Q6 How **concerned** are you about your illness?	6 (2)	5 (2)	59%[a]	5 (2)	65%[a]
Q7 How well do you feel you **understand** your illness?	2 (2)	2 (2)	36%	2 (1)	57%[a]
Q8 How much does your illness affect you **emotionally**?	6 (2)	5 (2)	59%[a]	6 (2)	48%

Q2 is removed, explanation in method section of this paper.
A higher score represents a more threatening view of the illness (Løchting G.K., 2013).
[a]Significant improvement (≤0.05), Wilcoxon signed-rank test.

healthcare professionals (nurse and social worker), rather than psychologists, who had a better understanding of practical aspects and challenges of intravenous home treatment. In our experience, the group format instead of an individual format promoted the understanding of metaphors. Discussing metaphors created more time to put these into perspective and relate these to their own life. Some limitations of the study need to be addressed. Starting with the design: a randomized control trial (RCT) is the recommend design for intervention studies.[23] In this case, the RCT design was considered unethical and infeasible: at inclusion, eligible patients experienced disease burden affecting daily life and were motivated to accept help. Providing a scam treatment or doing a crossover study was considered unethical as it includes making patients in need wait for help and could even increase problems. Therefore, a pre-post-test design was considered the most appropriate design in this population. Secondly, recruitment was challenging, resulting in extension of the recruitment period and a low response rate of 30% Although acceptance-related problems were frequently observed by the healthcare team, only patients who were burdened by acceptance problems were willing to participate. Furthermore, it was a difficult task to evaluate a qualitative intervention in a quantitative manner. Even in disease-specific questionnaires, some questions were perceived as confrontational. This was noted, but there is currently no solution to close the gap between patients' feelings or experiences and questionnaires.

These results were compared to other studies. Overall in chronic diseases, non-adherence is a big problem for which several adherence-specific interventions are available. Conn et al. [24] performed a systematic review and in a meta-analysis evaluated 771 interventions improving adherence behaviour outcomes. They reported that the most effective interventions were delivered face-to-face (mainly by pharmacists) and the largest effect sizes were found in medication electric event monitoring and pill counts. The overall conclusion was that healthcare providers should focus on behavioural strategies (habit-based) instead of cognitive strategies designed to change knowledge and beliefs.[24] The current intervention is a face-to-face intervention and this has certain components which could explain why this intervention turned out effective. There are two systematic reviews on ACT that have focused on the comparison with cognitive behaviour therapy rather than quantitative outcomes such as adherence.[13,25] Until now, there have been two adherence-specific intervention studies in haemophilia. Lock et al. conducted an pre- and post-test study evaluating home visits (6 visits in 2 years) by a haemophilia nurse, who educated children and parents.[26] In this population, the overall baseline adherence score was relatively high (VERITAS-Pro total normalized: 30) and VERITAS-Pro showed a significant improvement on the communication domain only (mean difference −1 point, $P = 0.03$). Cuesta-Barriuso et al conducted an cross-sectional descriptive study evaluating 'Medtep': an online platform[27] (eg information about infusions, physical activities and an infusion log). This study reported significant improvement on adherence (VERITAS-Pro) after 12 months: total score (mean difference −11 points, $P < 0.01$) and domain 'time', 'plan', 'remember', 'skip' and 'communicate' (mean difference ranging from −1.4 to −2.6

points, $P < 0.05$). This effect may be underestimated as only 56% used Medtep after 12 months.

The use of point of care ultrasound as visual feedback to promote adherence in patients with haemophilia is mentioned by some researchers, but a formal evaluation of the effects of point of care ultrasound on adherence is lacking.[28,29] A recently published abstract reported a significant improvement in VERITAS-Pro scores following monitoring with ultrasound and diaries.[30]

This study has clinical and research implications. Based on the positive results, we recommend to implement the ACT training on an annual basis. This time interval is recommended to create time to recruit patients. In our centre, we are currently expanding the training to all patients with clotting disorders with illness acceptance problems. Based on positive results of the ACT method in other chronic conditions (eg HIV, diabetes, parenting of children with chronic pain, brain injury and cancer[11,13]), we expect that these patients will benefit from this intervention too. Potential candidates should be aware of acceptance-related problems, and recruitment for the intervention is therefore most successful at the time the patient experiences problems. It is good to take into account that this training group not only reported improvement on mental domains of HRQoL but also in the physical domains (general health). The next research step will be to implement this training in daily health care including patients with other diagnoses and perform a cost-effectiveness evaluation.

5 | CONCLUSION

This study evaluated the effectiveness of and tailored acceptance intervention based on ACT. Clinically relevant and significant improvements in adherence, quality of life and illness perception were observed. Patients evaluated the training as positive and experienced the training as a personal enrichment and life-changing experience. The training will be implemented in haemophilia care in the Netherlands. Future research will focus on cost-effectiveness and exploring possibilities to implement this training in other clotting disorders.

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