Psychological interventions for people with hemophilia

Review information

Review type: Intervention

Review number: 0143

Authors

Laura Palareti[1], Giannino Melotti[1], Frederica Cassis[2], Sarah J Nevitt[3], Alfonso Iorio[4]

[1]Department of Education Studies "G.M. Bertin", University of Bologna, Bologna, Italy
[2]Hemophilia Centre of Hospital Das Clinicas, FMUSP, San Pablo, Brazil
[3]Department of Biostatistics, University of Liverpool, Liverpool, UK
[4]Department of Health Research Methods, Evidence and Impact (HEI), McMaster University, Hamilton, Canada

Citation example: Palareti L, Melotti G, Cassis F, Nevitt SJ, Iorio A. Psychological interventions for people with hemophilia. Cochrane Database of Systematic Reviews 2020 , Issue 3 . Art. No.: CD010215. DOI: 10.1002/14651858.CD010215.pub2 .

Contact person

Laura Palareti

Associate Professor in Social Psychology
Department of Education Studies "G.M. Bertin"
University of Bologna
Via Filippo Re, 6
Bologna
40126
Italy

E-mail: laura.palareti2@unibo.it

Dates

Assessed as Up-to-date: 11 February 2020
Date of Search: 13 June 2019
Next Stage Expected: 11 February 2022
Protocol First Published: Issue 11 , 2012
Review First Published: Issue 3 , 2020
Last Citation Issue: Issue 3 , 2020

What's new

Date	Event	Description

History

Date	Event	Description

Abstract

Background

Managing hemophilia is challenging both in terms of medical treatment and its broad impact on many aspects of the individual's life, including self-perception. Several psychosocial issues are potentially relevant in the clinical management of hemophilia, including it being a chronic and incurable condition; e.g. people with hemophilia must adapt to optimally interact with peers and to practice sports - even choosing a sport represents an issue for perceived limitations, expectations and cultural influences on the individual and their family. People with hemophilia can react by denying their condition and its manifestations and not adhering to treatment. Due to the complexity of relationships surrounding genetic diseases, parents and relatives may have their own issues that contribute to making life easier or more difficult for the person with hemophilia. Anxiety, sadness and depression resulting in mental health disorders are reported in this population and may influence quality of life (QoL) depending on cultural background, religious beliefs, family support and other variables.

Objectives

Primarily to assess the effectiveness of psychological therapies for improving the ability of people with hemophilia to cope with their chronic condition.

Search methods

We aimed to identify trials from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies

Trials Register, Embase and PsycINFO, CINAHL, MEDLINE and trial registries. We searched reference lists of included publications.

Most recent search of the Group's register: 13 June 2019.

Selection criteria

Randomized controlled trials (RCTs) and quasi-RCTs in people with hemophilia of any age or gender, type A or B, any severity, with or without inhibitors, with or without HIV or hepatitis C virus. All psychological interventions for promoting emotional, intellectual and spiritual wellness. Individual, group or family group therapy interventions were eligible.

Data collection and analysis

We independently assessed trials, extracted data and assessed the risk of bias and assessed the quality of the evidence using GRADE.

Main results

Seven trials were included (362 participants randomized, data from 264 participants available for analysis); six of parallel design and one a partial cross-over design. One multicenter trial was conducted in Canada; the remaining six were single centre undertaken in the UK, USA, Iran and in the Netherlands.

All trials had a high risk of bias for participant blinding and use of patient-reported outcomes.

Evidence was retrieved on four interventions: psycho-education (DVD plus information booklet versus information booklet alone; computerised learning versus no intervention); cognitive therapy (auto-hypnosis (self-hypnosis) versus control); and behavioural therapy (relaxation (progressive or self control) versus no treatment). We also aimed to assess psychodynamic therapy and systemic therapy, but no trials were identified.

Heterogeneity of the outcome measures and measurements precluded meta-analyses. No trial reported the cost of the psychological intervention and family adjustment.

DVD plus information booklet compared to information booklet alone

One trial (108 participants) showed coping strategies may lower pre-contemplation scores and negative thoughts, mean difference (MD) -0.24 (95%CI -0.48 - 0.00, low-certainty evidence), however, other measures of coping strategies in the same trial suggest little or no difference between groups, e.g. contemplation, MD (-0.09, 95%CI -0.32 - 0.14, low-certainty evidence). The same trial measured QoL and showed little or no difference between treatment groups for the physical domain, MD 0.59 (95% CI -3.66 to 4.84, low-certainty evidence), but may improve scores in the mental health domain for those receiving the booklet plus DVD compared to booklet alone, MD (4.70, 95% CI 0.33 to 9.07, low-certainty evidence). Mood or personal well-being were not reported.

Computerised learning compared to no intervention

Two trials (57 participants) reported on interventions aimed at children and adolescents and their impact on promoting a sense of self-efficacy (primary outcome 'Mood and personal well-being'), but only one showed an increase, MD 7.46 (95%CI 3.21 to 11.71, 17 participants, very low-certainty evidence); the second did not report control group data. One trial (30 participants) showed the intervention did not improve self-efficacy in adults, but appropriate data could not be extracted. Two trials (47 participants) reported coping strategies; one only reported within-group differences from baseline, the second showed an increase from baseline in coping strategies in the Internet program group compared to the no intervention group (disease-specific knowledge, MD 2.45 (95% CI 0.89 to 4.01); self-management ability and transition readiness, MD 19.90 (95% CI 3.61 to 36.19; low-certainty evidence).

One trial reported QoL but with insufficient information to calculate changes from baseline; no difference in post-treatment scores was seen between groups, MD -8.65, 95% CI -18.30 to 1.00, very low-certainty evidence).

Auto-hypnosis (self-hypnosis) compared to control

There were two older trials that reported on this intervention (50 participants) focusing mainly on the secondary outcome 'physical health'; only one trial reported the primary outcome ‘mood and personal well-being’ (only within-group differences in the treatment group). Coping strategies and QoL were not assessed in the trials.

Relaxation (progressive or self control) compared to no treatment

Only one trial (seven participants) from 1985, was included which focused on 'physical health' and did not report on any of our primary outcomes.

Authors' conclusions

Not all of the seven included trials analysed the effects of the interventions on our primary outcomes (mood and personal well-being, coping strategies and QoL).

Three trials were conducted in the 1970s and 1980s using techniques of auto-hypnosis or relaxation and, in accordance with the needs and therapeutic possibilities of the time, they focused on secondary outcomes, e.g. frequency of bleeding (physical health) and adherence to the intervention.

The four newer trials assessed psycho-educational interventions all mediated by the use of technologies (DVD or

computer) and often created according to age needs of the target group. In these cases, attention was shifted to our pre-defined primary outcomes.

This review has identified low- and very low-certainty evidence, prompting caution in its interpretation. The major problem we encountered was the heterogeneity of trial designs, of interventions and of outcome measures used across the trials. We strongly suggest that researchers consider developing a core outcome set to streamline future research; randomization was proven to be safe and acceptable, and blinding should be considered for those assessing patient-reported outcomes.

Plain language summary

Psychological interventions for people living with hemophilia

Review question

Do psychological interventions improve the quality of life in people with hemophilia?

Background

Hemophilia is an inherited bleeding disorder. Affected individuals bleed in their joints, and, if untreated, develop crippling joint damage occurring from recurrent joint bleeds. Depending on treatment availability, people living with hemophilia may or may not be able to enjoy a 'normal' or fulfilling life, and often present limitations in the range of physical activity, sports participation, family-life planning and undertaking education and work attainment. Psychological interventions are often claimed to be important in order to minimise the impact of hemophilia and its affect on the quality of life of individuals living with the condition.

Search date

The evidence is current to 13 June 2019.

Study characteristics

We included trials comparing people with hemophilia receiving any psychological intervention compared with other individuals receiving a different intervention or no intervention at all.

We found seven trials with 362 people with hemophilia aged between 6 and 65 years of age. Trials compared either a DVD plus information booklet or computerised learning or auto-hypnosis (self-hypnosis) or relaxation techniques to no treatment and people were selected for one treatment or the other randomly. The trials lasted from one to six months.

Key results

All treatments were safe, no major side effects were reported. Psycho-educational interventions in children and adolescents seemed to promote a sense of self-efficacy and better self-management skills, but the quality of the evidence suggests that more rigorous experimental design is required. One trial in adults did not show any effect. Self-hypnosis and relaxation techniques were not tested for the primary outcome but were useful in decreasing the number and severity of joint bleeds when drug treatment was not available. The effects of these interventions on quality of life vary. The major problem we encountered in this review is the difference in trial designs, interventions and outcome measures used across the trials. We strongly suggest that researchers in the field consider developing a core outcome set to streamline future research. Randomization was proven to be safe and acceptable in this research field, and blinding of outcome assessors should be considered in the presence of patient-reported outcomes.

Quality of the evidence

The overall quality of the evidence was low to very low.

Background

Description of the condition

A glossary of terms is available (Appendix 1).

Hemophilia A and B (Christmas Disease) are rare chronic and inherited blood clotting disorders (Lozier 2004; Rodgers 1999). Although hemophilia A and B are hereditary disorders, 30% to 40% of hemophilia cases are due to a spontaneous mutation, meaning that in such families there is no preceding history of hemophilia (Hoots 2007; Rodgers 1999).

Internationally, the treatment of hemophilia varies widely, dependent upon healthcare systems and infrastructure, governmental support and gross domestic product (GDP). In developing nations access to hemophilia care and treatment is limited and disability consequent upon hemophilia is greater and more frequent, with significant reduced life expectancy and societal integration. Therefore, relationships, understanding, opportunities and attitudes to hemophilia *per se* and to individuals with hemophilia vary nation to nation and healthcare system to healthcare system.

Clinically, hemophilia manifests through a wide and varied pattern of bleeding events. Most bleeding

events in severe and moderate hemophilia occur in the joints and muscles. Bleeds may also occur in other soft tissues (often associated with trauma), or with surgical or dental interventions or generally in the oral cavity (tongue and lips lesions) (Lozier 2004). Epistaxis, hematuria and gastro-intestinal and iliopsoas bleeding may also occur (Kessler 2006).

The primary consequence of hemarthrosis is the development of chronic hemophilic arthropathy, which may occur if hemarthroses are recurrent, untreated, or inadequately treated. Chronic hemophilic arthropathy results in deformity, impairment of joint movement, reduced mobility and chronic pain (Roosendaal 2006; Villaça 2004).

The standard medical treatment for hemophilia is factor replacement therapy, given by intravenous infusion either on demand (when the bleeding occurs) or, in those with severe hemophilia, prophylactically to prevent recurrent hemorrhage and so the development of chronic hemophilic arthropathy (Iorio 2011). Some individuals develop antibodies directed against missing or abnormal clotting factor that inhibit the effect of transfused factor concentrates. In the presence of such antibodies (inhibitors), management of both bleeding events and the hemophilia in general, is significantly more complex. Therapies to control bleeding are effective but very costly (Iorio 2010) and attempts to eradicate the inhibitors are an option to be considered.

Historically (until late 1980s), prior to the implementation of specific donor testing and the development of effective virus inactivation processes in the manufacture of plasma concentrates, many people with hemophilia acquired blood borne virus infections (HIV or hepatitis C (HCV), or both) through the use of large pool plasma-derived concentrates. This has been a significant legacy, physically and psychologically, of earlier generation plasma-derived factor concentrate treatments.

Besides medical treatment, management of hemophilia also represents a challenge due to the peculiarities of this inherited bleeding disorder. The ability to cope with the bleeding disorder and taking into account the self-perception of the individual are critical. Several psychosocial issues should be considered in the management of hemophilia, including the following.

- Hemophilia is a chronic and incurable condition, which requires each individual to have an adaptation process to be able to optimally interact with peers (Barlow 2007; Dunn 2008; Plug 2008; Remor 2002; Stieltjes 2009; Talaulikar 2006). For example, sports are recommended by the World Federation of Hemophilia (WFH), but the choice and practice represent a psychosocial issue that requires perception of limitations, expectations and cultural influences on the child and family, along with the advice by the hemophilia centers (Mulder 2004; von Mackensen 2007).
- Where treatment is available and prophylaxis is used, it is only when a bleed occurs or pain is felt, or when day-to-day activities are interrupted or restricted by the consequences of bleeding, that the person with hemophilia becomes aware of the disease and feels himself or herself as a patient. This fact can lead to a denial of the bleeding disorder, which is a commonly used mechanism, particularly in adolescence, and to non-adherence (Khair 2010; Penica 2008).
- Where treatment is unavailable, acute and chronic pain and arthropathy become an experience from childhood onwards. The development towards a functional and productive adult personality including undertaking studies and maintaining both employment and relationships can become issues (Barlow 2007; Elander 2009; Plug 2008; Siboni 2009).
- Parents and relatives, due to the highly demanding situation and the complexity of the relationships in the setting of a genetically transmitted disease, may have their own issues that contribute to making life easier or more difficult for the individual with the disorder (Beeton 2007; Emiliani 2010; Emiliani 2011).
- Feelings of anxiety, sadness and depression traducing in mental health disorders are reported in people with hemophilia, but will vary in their influence in the individual's quality of life (QoL) depending on cultural backgrounds, religious beliefs, family support and others variables (Cassis 2007; Ghanizadeh 2009)

Description of the intervention

Psychological interventions are used to help individuals with hemophilia deal better with the different psychological issues that they experience throughout their whole life cycle. These interventions can include family members such as parents and siblings. The interventions are carried out in either treatment centers, facilities linked to the medical team or a non-medical environment, such as a individuals' organization facility or any other community-based setting.

There are different types of interventions, distinguished based on the objectives to be achieved and on other characteristics, such as the individual's availability to frequently attend the center, or his or her physical and emotional wellness state.

These interventions include: cognitive therapy; psychodynamic psychotherapy; psycho-education; behavioural therapy; and systemic therapy.

How the intervention might work

A better functional status (as measured with objective instruments) and an improved QoL are expected as a result of the intervention. Physical limitations or impairment are not always correlated with a poor mental health quality (Stieltjes 2009) showing how important adaptive coping strategies are in coping with living with hemophilia issues. Reports on the importance of acceptance of hemophilia as part of self

are well documented (Albrecht 1999; Beeton 2005).

Parents can receive support through counselling, from the moment of diagnosis through the entire life cycle, with the aim of helping to understand each cognitive stage of development of their child (Bottos 2007). Children themselves can receive support through play therapy. This preventive approach aims to avoid: rejection of hemophilia; fear of reporting bleedings; and non-compliance (Cassis 2007).

One of the outcomes usually measured to assess the effect of psychosocial interventions is QoL. Different approaches have been undertaken with questionnaires to assess this outcome. Generic instruments such as SF-36 or EQ-5D can be used, or hemophilia specific ones. For children, CHO-KLAT is the most commonly used questionnaire (Young 2006); for children and adults the Haemo-QoL instrument (Remor 2002; von Mackensen 2004). QoL has also been studied in elderly individuals (Siboni 2009).

Why it is important to do this review

People with hemophilia, either mild, moderate, or severe, and with or without inhibitors, often present with the effects of psychosocial stressors. Psychological interventions to help coping with these psychosocial issues are often claimed to be helpful by several hemophilia healthcare professionals and patient organizations in many countries. Various schemes and programs to provide support on emotional, cognitive and educational grounds have been proposed by psychologists, social workers and counsellors. Although many different interventions have been used and papers on these published, a systematic review in the field of psychological therapies would provide a knowledge base illustrating which psychological therapies are often utilised and which are proven effective.

Objectives

The primary purpose of this review is to assess the effectiveness of psychological therapies for improving the ability of people with hemophilia to cope with their chronic condition.

The main objectives are to:

1. examine the effectiveness of psychological therapies for managing hemophilia;
2. determine which phase of the patient's life or phase of treatment, or both, affects the effectiveness of interventions;
3. determine which psychological therapies (as described under 'Types of interventions') are more effective for any given situation.

Methods

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and quasi-RCTs.

Types of participants

People with hemophilia of any age or gender, type A or B, any severity (severe, moderate, mild), with or without inhibitors. People with HIV and or HCV are eligible for inclusion.

Types of interventions

This review targets all psychological interventions which have the objective to promote emotional, intellectual and spiritual wellness. Individual, group or family group therapy interventions are eligible for inclusion. Family group therapy will be included if family members are participating with the patient.

The interventions we wish to explore are usually targeting: QoL; early understanding of the chronic condition (awareness and knowledge); adherence or compliance to treatment (on-demand or prophylaxis); inclusion in social life; and pain management (chronic or acute).

Psycho-education and low-intensity psycho-educational intervention (telephone, Internet, diaries as follow-up tools)

Psycho-education means providing information and learning about oneself and one's own treatment aiming to increase self-confidence for a better day-to-day life. It is also used to provide early coping strategies to the individual and his or her parents, and to deal with stressors linked to hemophilia and its impact on the individual's life. Psycho-education intervention are usually targeting one or more of the following.

- Management of treatment for hemophilia A and B (including those with inhibitors)
- Management of treatment for HIV or HCV, or both
- Self-infusion therapy programs for patients on-demand or on prophylaxis
- Port-a-cath maintenance
- Availability of Learning and counselling with educational tools

Cognitive therapy

- Investigate ways of thinking, perceiving and feeling (e.g. low self-esteem, misunderstandings)
- Inform and re-frame inappropriate thoughts or beliefs

- Monitoring thoughts, feelings
- Uses imagery visualization with hypnosis or self-hypnosis

Behavioural therapy

- Activity monitoring, re-organizing behaviours
- Relaxation therapy, visualization and biofeedback
- Communication skills training through flashcards, teach back
- Goal setting
- Decision making to solve problems

Psychodynamic psychotherapy

- Deal with the individual emotional, cognitive, physical development since childhood
- Investigate ways of thinking through the expression of dreams, fantasies, active imagination
- Re-signify traumatic and or painful experiences by having new insights into them

Systemic therapy

- Learning new approaches to cope with problems between members of the family
- The psychological frame can vary from psychodynamic, behavioural or interactional therapy

Types of outcome measures

Primary outcomes

1. Mood and personal well-being: any measure with adequate psychometric properties that identifies psychiatric symptomatology, emotional or behavioural difficulties in child or adult (e.g. anxiety and depression) as well as positive attitudes toward life and themselves (e.g. self-esteem, self-efficacy)
2. Coping strategies for relief of pain, anxiety, early report of bleeding, preparation for joint replacement and surgery, complications such as HCV and HIV, and adherence to treatment, including any measure of specific knowledge about the disease
3. QoL (any measure that quantifies the extent to which the child or adult is able to participate in developmentally appropriate social activities in the field of education, employment, leisure time)

Secondary outcomes

1. Compliance or adherence to the trial intervention (including intervention satisfaction)
2. Physical health including: reduction of bleedings and emergency department visits, hospital admissions, duration of hospitalisations, presence of co-morbidities, pain intensity
3. Cost (of psychological intervention)
4. Family adjustment

Search methods for identification of studies

We searched for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

The Cochrane Cystic Fibrosis and Genetic Disorders Group's Information Specialist conducted a search of the Group's Coagulopathies Trials Register for relevant trials using the following terms: haemophilia* AND (education OR psychology).

The Coagulopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE and the prospective handsearching of one journal - *Haemophilia*. Unpublished work is identified by searching the abstract books of major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Congress of the World Federation of Hemophilia; the European Association for Haemophilia and Allied Disorders, the American Society of Gene and Cell Therapy and the International Society on Thrombosis and Haemostasis. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

Date of the most recent search of the Group's Coagulopathies Trials Register: 13 June 2019.

We also searched the following databases and trial registries (Appendix 2):

- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; from 1982 to 07 June 2018);
- Clinical Trial Registry (US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov; searched 30 March 2018);
- Embase (from 1974 to 30 March 2018);
- MEDLINE Ovid (from 1946 to 07 June 2018);
- PsycINFO Ovid (from 1806 to 07 June 2018);

- WHO ICTRP (World Health Organization International Clinical Trials Registry Platform; searched 06 September 2019).

Searching other resources

We checked the bibliographies of included trials and any relevant systematic reviews, reports and dissertations identified for further references to relevant trials. We handsearched conference proceedings of the International Society for Thrombosis and Haemostasis from 1990 to 30 June 2017.

Data collection and analysis

Selection of studies

Two review authors (LP and FC or GM) independently assessed trial eligibility using a standardized form. We resolved any disagreements by discussion, or if unsuccessful, by asking a third author (AI or SN). When we identified multiple publications on the same trial we listed all these references together under one study identifier and used all available data.

Data extraction and management

Two review authors (LP, GM) independently performed data extraction using a standardized form. We resolved any disagreements by discussion, or if unsuccessful, by asking a third author (AI or SN). We extracted the following: bibliographical data (authors, journal, publication year, publication type); trial type; type of participants (patients, carriers, carers); number of participants, intervention(s) number; and type of comparator.

If required, the review authors planned to contact original trial authors to request any additional data not found in the publication from the trial authors. In particular, Elander provided clarification on the sample size of the trial via e-mail (Elander 2011), however, to date, we have been unsuccessful in contacting Beheshtipoor (Beheshtipoor 2015).

Where possible, we planned to group outcome data in the analyses as follows: short-term (on treatment); medium-term (end of treatment to three months); long-term (over three months). Where reported, within these categories, we noted the specific time point that the outcome data was recorded at (e.g. at three months, at six months).

Assessment of risk of bias in included studies

We used the standard risk of bias assessment tool incorporated in the RevMan software (RevMan 2014). We assessed the risk of bias over the five domains of:

- random sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting.

Two review authors (LP and GM) independently assessed the risk of bias and resolved any disagreements by discussion or, if unsuccessful, by asking a third author (AI or SN) to arbitrate. We judged there to be a low, unclear or high risk of bias for each of the domains listed above.

Measures of treatment effect

Where possible, for dichotomous outcomes (such as compliance), we calculated the risk ratio (RR) and their 95% confidence intervals (CI); and for continuous data (such as mood and personal well-being) we calculated the mean difference (MD) and their 95% CIs. If different scales were used to measure the same outcome (such as for QoL), we tried to calculate and report the standardized mean difference (SMD) and their 95% CIs.

Unit of analysis issues

The unit of analysis was the individual whenever possible; if we identify cluster-RCTs or cross-over RCTs in future updates of this review, we intend to check these for unit of analysis errors based on the advice given in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We aimed to conduct all analyses by intention-to-treat. Since we do expect the effect of treatment to progressively increase over time during treatment and to progressively decrease thereafter, we do not foresee that the last observation carried forward methods will apply. If we had encountered missing data which could not be retrieved by asking the trial authors, we planned, if possible, to perform a sensitivity analysis with the best and worst case scenario methods to assess the effect of the missing data.

Assessment of heterogeneity

We intended to investigate heterogeneity between trials through visual examination of the combined data presented in the forest plots and by using the I^2 statistic together with Chi^2 values and their CIs (Deeks 2011).

Ths I^2 measure describes the percentage of total variation across trials that are due to heterogeneity rather than by chance (Higgins 2003). The values of I^2 lie between 0% and 100%. We used a categorization of

heterogeneity according to the following values:

- not important (I^2 values 0% to 40%);
- moderate (I^2 values 30% to 60%);
- substantial (I^2 values 50% to 90%); and
- considerable (I^2 values 75% to 100%).

Assessment of reporting biases

We assessed the consistency of measurements and outcomes planned by the original Investigators during the trial and those reported within the published paper by comparing the trial protocols (when available) with the information in the final publication. Where protocols were not available, we compared the 'Methods' and the 'Results' sections of the published papers. We also used our knowledge of the clinical background to identify standard outcome measures usually taken, but not reported by the trial investigators.

For future updates, if we include a sufficient number of trials (10 or more), we will attempt to assess whether the review is subject to publication bias by using a funnel plot. If we detect asymmetry, we will explore causes other than publication bias.

Data synthesis

For included trials, we extracted data and entered them into RevMan (RevMan 2014). We used a fixed-effect model for the meta-analyses. For future updates, if we identify substantial or considerable heterogeneity (as defined above), we intend to explore potential causes of heterogeneity and to use a random-effects model. Where available data did not allow us to undertake meta-analyses, we have used a narrative approach to report results.

Subgroup analysis and investigation of heterogeneity

If sufficient numbers (at least 10 trials) are available in the future, we plan to investigate any heterogeneity we identify using subgroup analysis of potential confounding factors:

- treatment;
- age;
- inhibitor status;
- different phases of life: at diagnosis; during childhood, when learning self-infusion phase; at port-a-cath placement; after contracting or starting treatment for HCV or HIV (or both); at attainment of specific education levels.

Sensitivity analysis

For future updates, if possible, we plan to undertake sensitivity analyses to assess the robustness of our review results by repeating the analysis with the following adjustments:

- exclusion of trials with unclear or inadequate allocation concealment;
- exclusion of trials with unclear or inadequate blinding of outcomes assessment;
- exclusion of trials with unclear or inadequate completeness of follow-up.

Also as discussed above (Dealing with missing data), if we encountered missing data which could not be provided by original trial authors, we planned, if possible, to perform a sensitivity analysis with the best and worst case scenario methods to assess effect of the missing data.

Summary of findings and quality of the evidence (GRADE)

In a post hoc change from the protocol, we have presented four summary of findings tables, one for each comparison within the review (Summary of findings table 1; Summary of findings table 2; Summary of findings table 3; Summary of findings table 4).

1. DVD plus information booklet compared to information booklet alone for hemophilia
2. Computerised learning compared to no intervention for hemophilia
3. Auto-hypnosis (self-hypnosis) compared to control for hemophilia
4. Relaxation (progressive or self control) compared to no treatment for hemophilia

All primary and secondary outcomes of the review were included in these tables.

We determined the quality of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one trial, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by one level if we considered the limitation to be serious and by two levels if very serious.

For clarity in the tables, where outcomes were presented using different measures (e.g. physical health) or different domains (e.g. QoL), a general statement is made in the table regarding the summary of findings for these outcomes and the evidence is graded based on all of the measures or subdomains combined.

Results

Description of studies

Results of the search

Please refer to a figure that reports the flow diagram of the results of the searches (Figure 1).

A total of 595 references were identified through searches of the Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register, MEDLINE, Embase, PsychINFO, CINAHL, ClinicalTrials.gov and the WHO ICTRP. A further 25 additional references were identified through other sources, giving a total of 620 references potentially relevant for inclusion. After removing 75 duplicates, we assessed the remaining 545 references; 498 references did not meet the inclusion criteria, leaving 47 references (to 34 trials) for inclusion in this review.

We included seven trials (16 references) for synthesis (Beheshtipoor 2015; Breakey 2014; Elander 2011; LaBaw 1975; Lichstein 1985; Mulders 2012; Swirsky-Sacchetti 1986). We excluded 21 trials (24 references) (Beheshtipoor 2012; Cuesta-Barriuso 2014; Cuesta-Barriuso 2018; Dunne 1991; Firoozabadi 2012; Heydari 2018; ISRCTN63283043; Kang 2012; Magli-Barioz 2004; NCT02198014; NCT02825706; NCT03136003; Omura 2013; Parsons 2000; Penica 2008; Sergis-Deavenport 1983; Slifer 2009; Thomas 2001; Von Mackensen 2012; Walker 2004; Wincott 1976).

Four trials (five references) are ongoing (IRCT201502079267N4; IRCT20180311039037N1; NCT03529474; Pinto 2016); two are awaiting classification, one is currently published in conference proceedings and we aim to further assess when this is published as a full-text (Karimi 2014); the second is a full-text paper in Korean that is awaiting translation (Kang 2005).

Included studies

The seven included trials were published in peer-reviewed journals (Beheshtipoor 2015; Breakey 2014; Elander 2011; LaBaw 1975; Lichstein 1985; Mulders 2012; Swirsky-Sacchetti 1986). Multiple records for two of the trials were identified: one was reported in two journal articles (Elander 2011), and one was reported in two conference proceeding abstracts, one protocol in ClinicalTrials.gov and one journal article (Breakey 2014). For the Elander trial, data were extracted from the earlier and most complete publication and then from the most recent publication as necessary (Elander 2011).

Study design

Six trials were of parallel design (Beheshtipoor 2015; Breakey 2014; Elander 2011; LaBaw 1975; Mulders 2012; Swirsky-Sacchetti 1986) and one was a partial cross-over design (Lichstein 1985). One trial was conducted in Canada and was multicenter (Breakey 2014); all the others were single centre and were undertaken in the UK (Elander 2011), the USA (LaBaw 1975; Lichstein 1985; Swirsky-Sacchetti 1986), Iran (Beheshtipoor 2015) and in The Netherlands (Mulders 2012).

Participants

A total of 362 participants were recruited and randomized across seven trials and 264 participants from these seven trials were included in our analysis (see Incomplete outcome data (attrition bias) and Characteristics of included studies).

Two trials (79 participants) included only children or adolescents with hemophilia. In particular, one included children between eight and 12 years old (Beheshtipoor 2015), while the second included adolescents between 12 and 18 years of age (Breakey 2014). Two trials (50 participants) included children and adults aged between five and 50 years old (LaBaw 1975; Swirsky-Sacchetti 1986). The 30 participants in the Mulders trial were aged between 17 and 67 years old (Mulders 2012). Two trials included 203 adults over 20 years of age (Lichstein 1985; Elander 2011).

All participants were males with the exception of three females included in the Beheshitpoor trial (Beheshtipoor 2015). The majority of trials were not restricted to specific severity or types of hemophilia, however, the Swirsky-Sacchetti trial included only severe forms of the disease (Swirsky-Sacchetti 1986) and inclusion trial for the Lichstein trial was that participants had to have at least 0.5 bleeds per week over the past two years (Lichstein 1985).

Interventions

Psycho-education and low-intensity psycho-educational intervention (telephone, Internet, diaries as following up tools)

a. DVD plus information booklet compared to information booklet alone

One trial, recruiting 196 participants, compared a DVD intervention for the self-management of joint pain plus an information booklet to the information booklet alone (Elander 2011). The hypothesis is that using a DVD is more effective because it maximizes viewer engagement and can be easily used at home. The trial report presented results from a series of questionnaires at baseline and after six months of treatment. Further analyses evaluated the impact of the DVD among participants with different levels of education to assess the extent to which receiving the DVD improves QoL, specifically for those with less education.

b. Computerised learning compared to no intervention

Three trials, recruiting a total of 109 participants, compared computerised learning (an e-learning program (Mulders 2012), computerised educational games (Beheshtipoor 2015) and an Internet-based

self-management and transitional care program (Breakey 2014)) to no intervention.

Cognitive therapy

a. Auto-hypnosis (self-hypnosis) compared to control

Two trials, recruiting a total of 44 participants, compared auto-hypnosis (self-hypnosis) to a control treatment (usual care (LaBaw 1975), and delayed intervention (Swirsky-Sacchetti 1986)).

Behavioural therapy

a. Relaxation (progressive or self control) compared to no treatment

One trial, recruiting seven participants, compared relaxation (progressive or self control) to no treatment (Lichstein 1985). The trial had a partial cross-over design; after two months of treatment, all participants crossed over onto the most effective treatment (self-control relaxation) and continued to be followed up. Results presented below apply only to the first two months of the trial, prior to cross-over.

Psychodynamic psychotherapy

No included trials made this comparison.

Systemic therapy

No included trials made this comparison.

Outcomes

Psycho-education and low-intensity psycho-educational intervention (telephone, Internet, diaries as following up tools)

a. DVD plus information booklet compared to information booklet alone

In the Elander trial two primary and one secondary outcomes relevant to this review were assessed (Elander 2011). For the primary outcome coping strategies, the authors reported on three questionnaires: the Pain Stages of Change Questionannaire (PSOCQ) (to measure the readiness to self-manage pain); the Hemophilia Pain Coping Questionnaire (Elander 2008) (to measure coping with pain and negative thoughts about pain); and the Chronic Pain Acceptance Questionnaire (McCracken 2004) (to measure the extent to which individuals are able to desist from attempts to avoid or reduce their chronic pain). For the second primary outcome of health-related QoL using the RAND 36 questionnaire and reported on both the physical and mental domain (Hays 1993; Hays 2001). The secondary outcome of compliance was assessed at follow-up when participants were asked how often they had watched the DVD or read the booklet, using 7-point response scales. They also rated the helpfulness of the DVD or booklet using 4-point scales. A further secondary outcome of physical health was assessed by rating pain intensity in the last month on a 10-cm visual analogue scale labelled "no pain" to "worst pain possible".

b. Computerised learning compared to no intervention

All three trials reporting on this intervention reported on the primary outcome of mood and personal well-being (Breakey 2014; Mulders 2012; Beheshtipoor 2015). Two trials assessed changes in the generalized self-efficacy using two non-identical versions of the General Self-Efficacy Scale of Sherer (GSE-S) (Sherer 1982) (17 items Breakey 2014; 12 items Beheshtipoor 2015). One trial assessed changes in the self-efficacy to perform home treatment using a non-validated scale adapted by Lee (Lee 1994) (Mulders 2012). The second primary outcome of coping strategies was considered in two studies (Breakey 2014; Mulders 2012). Adolescents' perceived medical self-management abilities and readiness for transition was measured pre and post intervention using the Self-Management Skills Assessment Guide (Williams 2011) (Breakey 2014). Both trials assessed knowledge about the disease and its treatment using ad hoc questionnaires (Breakey 2014; Mulders 2012). One trial also used a structured observation to rate patient performance in preparing and performing intravenous injections of clotting factor concentrates (Mulders 2012). Only one trial assessed the impact of his program on the third primary outcome of QoL (Breakey 2014); authors used the Canadian Haemophilia Outcomes-Kids' Life Assessment Tool (CHOK-LAT) (Young 2006). Only one trial reported on any of our secondary outcomes; Breakey reported adolescents' compliance and satisfaction with the Internet program using a brief questionnaire that explored (i) satisfaction with the health coach, (ii) satisfaction with website components and (iii) overall satisfaction with the website (Breakey 2014).

Cognitive therapy

a. Auto-hypnosis (self-hypnosis) compared to control

Two trials reported on this comparison; in one trial no primary outcome and only one secondary outcome relevant to this review were assessed (physical health) (LaBaw 1975), in the second trial one primary and two secondary outcomes relevant to this review were assessed (Swirsky-Sacchetti 1986). For the primary outcome mood and personal well-being, Swirsky-Sacchetti evaluated changes in the general distress level using the SCL-90 (Derogatis 1977) (Swirsky-Sacchetti 1986). Swirsky-Sacchetti also measured the secondary outcome of compliance using daily trance usage through participants' self-report diaries (Swirsky-Sacchetti 1986) and the hypnotic susceptibility of participants with the HGSHS:a (Shor 1962). Both trials reported on the reduction of bleedings and emergency department visits (secondary outcome of physical health). LawBaw assessed changes in the number of bags of blood (90 AHF each) used

by patients each year (LaBaw 1975); Swirsky-Sacchetti measured changes in terms of units of factor concentrate/kg of body weight/month (Swirsky-Sacchetti 1986).

Behavioural therapy

a. Relaxation (progressive or self control) compared to no treatment or each other

One trial reported on this comparison and provided results on one primary outcome and two secondary outcomes relevant to this review (Lichstein 1985). For the primary outcome of mood and personal well-being, data on daily tension were recorded during treatment and during follow-up (not at baseline) using a five points scale from 0 (= no tension experienced) to 5 (= tension ruined the whole day). For the secondary outcome of compliance, participants recorded the date and duration of home relaxation practice on forms conveniently designed for this purpose. Moreover, telephone inquiries were made without advance notice to participants' spouses, who were asked about the participants' attitudes toward relaxation and the extent of their daily practice. Authors also report data on treatment credibility rated by participants in the first session only, after they were presented with the therapeutic rationale. After each session participants rated the therapist's attitude in terms of skill, concern, and belief in the efficacy of treatment on separate 10-point scales. A further secondary outcome of physical health was assessed by: a reduction of bleedings and of emergency department visits (number of bleeds per week during baseline, intervention and follow-up were counted and the units of factor replacement used per week were recorded); and by pain intensity (during treatment and follow-up participants rated the highest degree of arthritic pain and bleeding pain experienced in each episode on a separate 5-point scales (0 = no pain, 5 = pain present, could not be ignored, bed rest required), adapted from Budzynski (Budzynski 1973)).

Psychodynamic psychotherapy

No trials referred to this type of intervention.

Systemic therapy

No trials referred to this type of intervention.

Excluded studies

We excluded 21 studies. In three studies the pre- and post- analyses were performed on a single group (Beheshtipoor 2012; Dunne 1991; Magli-Barioz 2004); one was a single-case study (Penica 2008); five were not RCTs (Cuesta-Barriuso 2014; Heydari 2018; Omura 2013; Parsons 2000; Sergis-Deavenport 1983); two were narrative papers that described interventions but did not report on any trial (Thomas 2001; Wincott 1976); in one the intervention targeted only mothers of children with hemophilia (Kang 2012) and another targeted nurses (ISRCTN63283043); seven did not match the inclusion criteria with regards to the type of intervention (Cuesta-Barriuso 2018; Firoozabadi 2012; NCT02198014; NCT02825706; NCT03136003; Von Mackensen 2012; Walker 2004); one was an RCT in people with chronic illness where the only two participants with hemophilia were in the same group (Slifer 2009).

Studies awaiting classification

Two studies are awaiting classification (Kang 2005; Karimi 2014). One is currently published in conference proceedings and we aim to further assess when this is published as a full-text (Karimi 2014); the second is a full-text paper in Korean that is awaiting translation (Kang 2005).

Ongoing studies

There are four ongoing trials (IRCT201502079267N4; IRCT20180311039037N1; NCT03529474; Pinto 2016).

Risk of bias in included studies

Allocation (selection bias)

Sequence generation was judged to be low risk in five of the trials (Beheshtipoor 2015; Breakey 2014; Elander 2011; Mulders 2012; Swirsky-Sacchetti 1986) and was judged as unclear for two trials (LaBaw 1975; Lichstein 1985).

Allocation concealment was judged to be low in three trials (Elander 2011; Mulders 2012; Swirsky-Sacchetti 1986) and unclear in the remaining four trials (Beheshtipoor 2015; Breakey 2014; LaBaw 1975; Lichstein 1985).

Blinding (performance bias and detection bias)

All trials were judged at high-risk bias for lack of participant blinding and concomitant use of patient-reported outcomes. However, the psychological nature of the intervention itself makes it difficult, if not impossible, to set up trials with blinded participants.

The blinding of personnel involved was judged unclear for five trials (Beheshtipoor 2015; Breakey 2014; Elander 2011; Mulders 2012; Swirsky-Sacchetti 1986), while for two there was a high risk of bias (LaBaw 1975; Lichstein 1985).

No trial openly specified if the outcome assessors were blinded, therefore, the risk of detection bias is considered unclear for all seven trials.

Incomplete outcome data (attrition bias)

Four trials have a low risk of bias and report 0% attrition, following up all randomized participants (Beheshtipoor 2015; LaBaw 1975; Lichstein 1985; Mulders 2012). Three trials were judged to be at a high risk of attrition bias given they lost 30% or more of the randomized participants (Breakey 2014; Elander 2011; Swirsky-Sacchetti 1986). Specifically, in the Breaky trial, more than 56% of participants did not complete the Breakey trial; however, it was a pilot study aimed at assessing the feasibility of an RCT and included the assessment of attrition problems (Breakey 2014). The Elander trial expected only 25% attrition, but encountered a much greater percentage due to dropouts (30.6%) and missing data (14.3%) (Elander 2011). Finally, the Swirsky-Sacchetti trial reported a 30% attrition, due both to dropouts (20%) and the development of inhibitors in three participants (10%) who were excluded from the evaluation of the outcome (amount of factor used) (Swirsky-Sacchetti 1986).

Selective reporting (reporting bias)

One trial was judged to be at low risk of selective reporting bias (Breakey 2014), and another to be at a high risk (Beheshtipoor 2015); the remaining five trials were considered to have an unclear risk of bias since we could not access the protocols (Elander 2011; LaBaw 1975; Lichstein 1985; Mulders 2012; Swirsky-Sacchetti 1986).

In Beheshitpoor trial, the data were reported in a partial and confusing way, and there were often inconsistencies between tables, text and abstract (Beheshtipoor 2015). The mean scores of both groups are reported but not all the standard deviations (SDs). The author has yet to respond to our request for clarification of the information and results in the paper.

Other potential sources of bias

No other sources of bias were identified, although In one trial, it was unclear whether more than 40 participants were eligible and also how the enrolment was managed (Beheshtipoor 2015). The attempts to contact the trial author to clarify this point were unsuccessful.

Effects of interventions

The quality of the evidence has been graded for those outcomes included in the summary of findings table. For the definitions of these gradings, please refer to the summary of findings tables (Summary of findings table 1; Summary of findings table 2; Summary of findings table 3; Summary of findings table 4).

Psycho-education and low-intensity psycho-educational intervention (telephone, Internet, diaries as following up tools)

a. DVD plus information booklet compared to information booklet alone

One trial compared a DVD intervention for the self-management of joint pain plus an information booklet to the information booklet alone in 108 participants out of 196 randomized participants (Elander 2011). The report presents results from a series of questionnaires in terms of the baseline measurement and measurements after six months of treatment.

Primary outcomes

1. Mood and personal well-being

The trial did not report this outcome (Elander 2011).

2. Coping strategies

a. Pain Stages of Change Questionannaire (PSOCQ)

In referring to the motivational model of Jensen the authors measured the readiness to self manage pain using the PSOCQ (Jensen 2003; Kerns 1997).

i. Precontemplation

Data at six months showed significantly lower scores in pre-contemplation for those who received the booklet plus the DVD compared to those who only received the booklet, MD −0.24 (95% CI −0.48 to 0.00) (P = 0.05) (low-certainty evidence) (Analysis 1.1).

ii. Contemplation

Data at six months showed no significant difference between treatment groups in terms of contemplation, MD −0.09 (95% CI −0.32 to 0.14) (P = 0.45) (low-certainty evidence) (Analysis 1.1).

iii. Action or maintenance

Data at six months showed no significant difference between treatment groups in terms of action or maintenance, MD 0.04 (95% CI −0.18 to 0.26) (P = 0.72) (Analysis 1.1).

b. Haemophilia Pain Coping Questionnaire

i. Active coping

Data at six months showed no significant difference between treatment groups in terms of active coping,

MD −0.34 (95% CI −0.75 to 0.07) (P = 0.10) (Analysis 1.2).

ii. Negative thoughts

Data at six months showed significantly lower scores in negative thoughts for those who received the booklet plus DVD compared to those who only received the booklet, MD −0.69 (95% CI −1.16 to −0.22) (P = 0.004) (Analysis 1.2).

iii. Passive adherence

Data at six months showed no significant difference between treatment groups in terms of passive adherence, MD −0.31 (95% CI −0.81 to 0.19) (P = 0.23) (Analysis 1.2).

c. Chronic Pain Acceptance Questionnaire

i. Activity engagement

Data at six months showed no significant difference between treatment groups in terms of activity engagement, MD 3.50 (95% CI −0.27 to 7.27) (P = 0.07) (Analysis 1.3).

ii. Pain willingness (recognition that avoidance and control are often unworkable methods of adapting to chronic pain)

Data at six months showed no significant difference between treatment groups in terms of pain willingness, MD 2.34 (95% CI −1.22 to 5.90) (P = 0.20) (Analysis 1.3).

3. QoL

The trial assessed health-related QoL using the RAND 36a questionnaire (Elander 2011).

a. Physical domain

Data at six months showed no significant difference between treatment groups in terms of the physical domain, MD 0.59 (95% CI −3.66 to 4.84) (P = 0.79) (low-certainty evidence) (Analysis 1.4).

b. Mental domain

Data at six months showed significant higher scores in the mental health domain for those who received the booklet plus DVD compared to those who only received the booklet, MD 4.70 (95% CI 0.33 to 9.07) (P = 0.035) (low-certainty evidence) (Analysis 1.4).

Secondary outcomes

1. Compliance or adherence to the trial intervention (including satisfaction for it)

Data at six months showed no significant differences in compliance or adherence to the trial intervention, RR 1.02 (95% CI 0.81 to 1.28) (P = 0.89) (low-certainty evidence) (Analysis 1.5) evaluated by categorizing participants in users of the intervention (those who watched or read the DVD or booklet, or both, at least once) and non-users (those that reported not looking at the DVD or booklet at all or not watching or reading them properly) (Elander 2011).

The 57% of those who received the DVD and 66% of those who watched it at least once, rated it as helpful.

2. Physical health

Elander did not report on any of the following outcomes: reduction of bleedings and emergency department visits; hospital admissions, duration of hospitalisations; and the presence of co-morbidities (Elander 2011).

a. Pain intensity

Elander used a visual analogue scale to report pain intensity (post treatment scores). Data at six months showed no significant difference between groups, MD −0.28 (95% CI −1.27 to 0.71) (P = 0.58) (low-certainty evidence) (Analysis 1.6).

3. Cost of psychological intervention

The included trial did not report this outcome (Elander 2011).

4. Family adjustment

The included trial did not report this outcome (Elander 2011).

b. Computerised learning compared to no intervention

Three trials recruiting a total of 109 participants compared computerised learning (an e-learning program (Mulders 2012), a computerised educational games on self-efficacy (Beheshtipoor 2015) and an Internet-based self-management and transitional care program (Breakey 2014)) to no intervention. Two trials included all randomized participants in their analyses (Beheshtipoor 2015; Mulders 2012), but only 17 out of 39 participants who completed the third trial were analysed (Breakey 2014). Therefore, up to 87 participants are assessed in this comparison.

One trial reported post-intervention results within the computerised educational games group only; no results for the control group were reported (Beheshtipoor 2015). Therefore, results of this trial cannot be included in the analyses and the results within the intervention group are reported

narratively (Beheshtipoor 2015).

Primary outcomes

1. Mood and personal well-being

Breakey reported self-efficacy using a reduced version of the GSE-S (GSE-S 12) (Bosscher 1998). The trial report presents pre-program and post-program scores, as well as within-group P values for the change within the groups. Therefore, we were able to calculate change from baseline measurements. We note that results presented in this review are different from the results presented in the Breakey report (Breakey 2014).

Data showed a significant increase from baseline in self-efficacy in the Internet program group compared to the no intervention group, MD 7.46 (95% CI 3.21 to 11.71) (17 participants) (P = 0.0006) (Analysis 2.1).

Beheshitpoor assessed self-efficacy using the GSE (1982) (Beheshtipoor 2015). The mean self-efficacy scores before, after and one month after intervention (20 participants) were 53.25 (SD 13.13), 60.95 (no SD reported), 60.90 (no SD reported) in the intervention group.

Using a five-question questionnaire (Lee 1994), Mulders reported only medians and ranges for all participants for this outcome. Therefore, data could not be included in the analysis, no significant differences in self-efficacy were observed between the intervention and the control group, either at start of the trial (P = 0.708) and after one month (P = 0.558) (30 participants) (Mulders 2012).

The evidence presented for this outcome was of very low certainty.

2. Coping strategies

The Beheshitpoor trial did not report on this outcome (Beheshtipoor 2015).

a. Disease-specific knowledge

Breakey assessed disease-specific knowledge through the 'Haemophilia Knowledge Questionnaire' and self-management ability and transition readiness through the 'Self-Management Skills Assessment Guide' (Breakey 2014). The trial reports present a pre-program and post-program score as well as within-group P values for the change within the groups. Therefore, we were able to calculate the change from baseline measurements. We note that, for this reason, results presented in the review are different from the results presented in the Breakey report (Breakey 2014). Data showed a significant increase from baseline in both disease-specific knowledge, MD 2.45 (95% CI 0.89 to 4.01) (P = 0.002) (Analysis 2.2) and self-management ability and transition readiness, MD 19.90 (95% CI 3.61 to 36.19) (P = 0.02) (Analysis 2.3) in the Internet program group compared to the no intervention group.

Data for analysis in the format required for the review could not be extracted from the Mulders published paper, therefore, we report the results published by the author about the impact of the e-learning program on self-injection practical skills and on disease-specific knowledge (Mulders 2012). Before treatment, the intervention group and the control group did not differ on either variables. After treatment, the intervention group improved significantly on both practical skills (P = 0.003) and knowledge (P = 0.001) (paired-sample t-tests) and showed higher scores than the control group (independent sample t-test: practical skills P = 0.002; knowledge P = 0.001). Paired sample t-tests for the control group did not show significant changes.

The evidence presented for this outcome was of low certainty.

3. QoL

Two trials did not report on this outcome (Beheshtipoor 2015; Mulders 2012).

Breakey reported health-related QoL according to the the CHOK-LAT (Breakey 2014). The trial reports present a pre-program and post-program score but there was insufficient information to calculate the change from baseline. Therefore, results presented are post-treatment scores. Data showed no significant difference between treatment groups in terms of QoL, MD -8.65 (95% CI -18.30 to 1.00) (P = 0.08) (very low-certainty evidence) (Analysis 2.4)

Secondary outcomes

1. Compliance or adherence to the trial intervention (including intervention satisfaction)

Beheshitpoor and Mulders did not report this outcome (Beheshtipoor 2015; Mulders 2012).

Breaky reported a good participation of adolescents in the experimental group to the Internet program and a general satisfaction for it (very low-certainty evidence) (Breakey 2014). For instance, all the 12 adolescents (100%) completed all eight learning modules and logged in for an average of 50 min each week (range = 25 to 120 min). Further information about program satisfaction can be found in the Breakey paper (Breakey 2014).

2. Physical health

None of the trials reported on this outcome (Beheshtipoor 2015; Breakey 2014; Mulders 2012).

3. Cost of psychological intervention

None of the trials reported on this outcome (Beheshtipoor 2015; Breakey 2014; Mulders 2012).

4. Family adjustment

None of the trials reported on this outcome (Beheshtipoor 2015; Breakey 2014; Mulders 2012).

Cognitive therapy

a. Auto-hypnosis (self-hypnosis) compared to control

Two trials recruiting a total of 50 participants compared auto- or self-hypnosis to a control treatment (usual care in the LawBaw trial (LaBaw 1975), delayed intervention in the Swirsky-Sacchetti trial) (Swirsky-Sacchetti 1986). All participants were included in the analysis in the LaBaw trial (LaBaw 1975) and 24 out of 30 randomized participants were included in the analysis in the Swirksy-Sacchetti trial (Swirsky-Sacchetti 1986). Therefore, up to 44 participants are assessed in this comparison.

Primary outcomes

1. Mood and personal well-being

One trial did not report this on this outcome (LaBaw 1975).

The second trial reported on changes in distress for the treatment group (n = 13) as measured by the SCL-90 from pre-test to follow-up (Swirsky-Sacchetti 1986). In particular, the General Severity Index (GSI) and the subscales measuring anxiety, depression, hostility, phobic anxiety, and obsessive-compulsivity were significantly reduced (Wilcoxon t-test) (very low-certainty evidence). Furthermore authors noticed a trend suggesting that those participants with higher GSI in the pre-test tended to profit more from treatment.

No results were reported for the control group of the Swirsky-Sacchetti trial (Swirsky-Sacchetti 1986).

2. Coping strategies

Neither trial reported on this outcome (LaBaw 1975; Swirsky-Sacchetti 1986).

3. QoL

Neither trial reported on this outcome (LaBaw 1975; Swirsky-Sacchetti 1986).

Secondary outcomes

1. Compliance or adherence to the trial intervention (including intervention satisfaction)

The LaBaw trial did not report on this outcome (LaBaw 1975).

In the case of the Swirsky-Sacchetti trial, even if the frequency of self-hypnosis was self-recorded on daily diaries, the authors did not provide information about how much the participants used self-hypnosis in their daily lives during the follow-up period (Swirsky-Sacchetti 1986). Authors also report that no correlation was found between hypnotizability of participants (measured by the Harvard Group Scale of Hypnotic Susceptibility) and treatment effect (very low-certainty evidence).

2. Physical health

Neither trial reported on any of the following outcomes: hospital admissions, duration of hospitalisations and the presence of co-morbidities or pain intensity (LaBaw 1975; Swirsky-Sacchetti 1986).

a. Reduction of bleedings and emergency department visits

One trial reported the number of bags of blood used by each participant before treatment and during three 10-month treatment periods, where a bag of blood equalled 90 AHF units (LaBaw 1975). The authors present medians due to the 'variability' of data. While it is difficult to accurately assess whether data are skewed (with only 10 participants in each group), we are satisfied that the distribution of the change from baseline in number of bags of blood used at each time point is approximately normally distributed, therefore, from the individual participant data available within the LaBaw report, we have calculated mean values which are presented in the analysis section (Analysis 3.1) (LaBaw 1975). We note that these results quoted below are different to the results quoted in the original report (LaBaw 1975).

Data showed a significant decrease in the number of bags of blood used in the treatment group compared to the control group during the first 10-month treatment period, MD -71.40 bags (95% CI -127.65 to -15.15) (P = 0.01), and during the second 10-month treatment period, MD -99.40 bags (95% CI -166.08 to -32.72) (P = 0.004) but not during the third 10-month treatment period, MD -51.70 bags (95% CI -163.15 to 59.75) (P = 0.36) (low-certainty evidence) (Analysis 3.1).

However, across the total 30 months (the first, second and third 10-month periods), there was significant decrease in number of bags of blood used in the treatment group compared to the control group, MD -74.17 bags (95% CI -141.14 to -7.19) (P = 0.03) (Analysis 3.1).

The second trial presented the mean factor usage scores (units/kg/month) for each participant pre- and post-treatment (and change values) (Swirsky-Sacchetti 1986). The authors present mean values, however we are concerned about the skewed distribution of the change values so we have presented values for the median and range. In the self-hypnosis treatment group, the median change in factor usage was a reduction of 19.84 (ranging from a reduction of 72.18 to an increase of 308.3

units/kg/month) and in the control group, the median change in factor usage was an increase of 10.31 (ranging from a reduction of 27.50 to an increase of 120.79 units/kg/month). The difference between groups was reported to be significant in the original trial report ($P < 0.05$ of Mann Whitney U test) (low-certainty evidence) (Swirsky-Sacchetti 1986). The authors report that there was a significant correlation indicating that participants who practised self-hypnosis more often were more likely to have decreased factor usage.

3. Cost of psychological intervention

Neither trial reported on this outcome (LaBaw 1975; Swirsky-Sacchetti 1986).

4. Family adjustment

Neither trial reported on this outcome (LaBaw 1975; Swirsky-Sacchetti 1986).

Behavioural therapy

a. Relaxation (progressive or self control) compared to no treatment or each other

One trial, recruiting seven participants, compared relaxation (progressive or self-control) to no treatment (Lichstein 1985). The trial had a partial cross-over design; after two months of treatment, all participants crossed over onto the most effective treatment (self-control relaxation) and continued to be followed up. Results presented below apply only to the first two months of the trial, prior to cross-over.

Primary outcomes

1. Mood and personal well-being

The trial did not report on this outcome (Lichstein 1985).

2. Coping strategies

The trial did not report on this outcome (Lichstein 1985).

3. QoL

The trial did not report on this outcome (Lichstein 1985).

Secondary outcomes

1. Compliance or adherence to the trial intervention (including satisfaction for it)

Date and duration of home relaxation practice was self-recorded. Authors report that the frequency of progressive or self-control relaxation practice was roughly comparable between groups and across phases (mean range, 0.9 to 1.4 per day), and therefore they consider participants were highly compliant with assignments (very low-certainty evidence). Authors also report that "empirical analyses of relaxation practice data present no detectable relationship between relaxation practice and any of the dependent measures." (Lichstein 1985, p. 159). Relaxation practice compliance was also checked through telephone inquiries made without advance notice to participants' spouses, confirming the positive attitude toward relaxation and its practice during the treatment and follow-up periods.

2. Physical health

Lichstein did not report on any of the following outcomes: hospital admissions; duration of hospitalisations; and the presence of co-morbidities or pain intensity (Lichstein 1985).

a. *Reduction of bleedings and emergency department visits*

The included trial reported the mean bleeding frequency per week and the mean factor replacement units per week (Lichstein 1985). Individual participant data were presented graphically for the mean bleeding frequency per week, therefore, the change from baseline after two months (prior to cross-over of treatments) was calculated and presented in the analyses (Analysis 4.1; Analysis 5.1; Analysis 6.1).

i. Reduction in number of bleeds per week

Data comparing progressive relaxation to no treatment showed no significant difference for the change in the number of bleeds per week between the two groups, MD 0.18 (95% CI −0.30 to 0.66) ($P = 0.46$) (very low-certainty evidence) (Analysis 4.1). Likewise, data comparing self-control relaxation to no treatment showed no significant difference in the change in the number of bleeds per week between the two groups, MD −0.32 (95% CI −1.20 to 0.56) ($P = 0.48$) (very low-certainty evidence) (Analysis 5.1). Also, when comparing the two active treatments, there was no significant difference in the change in the number of bleeds per week between progressive relaxation and self-control relaxation, MD 0.50 (95% CI −0.48 to 1.48) ($P = 0.32$) (very low-certainty evidence) (Analysis 6.1).

ii. Factor replacement

For mean factor replacement units per week, mean values only were presented without SDs or CIs therefore data could not be entered into the analysis. The authors state that "graphical data on factor replacement closely parallel those on bleeding frequency and are therefore not included". In the self-control relaxation group, a mean reduction of 382 units was reported compared to baseline and in the progressive relaxation group a mean reduction of 319 units was reported compared to baseline. Change from baseline was not reported in the control (no treatment group).

b. Pain

Comparing baseline, treatment, and follow-up periods for the variables daily tension, arthritic pain and bleeding pain, the authors couldn't "discern any pattern of progressive or self-control relaxation influence these ratings" (Lichstein 1985, p. 159). Daily tension ratings in the three phases ranged from 1.5 to 1.7, arthritic pain ratings ranged from 1.3 to 1.8, and bleeding pain ratings ranged from 2.8 to 3.5.

3. Cost of psychological intervention

The trial did not report this outcome (Lichstein 1985).

4. Family adjustment

The trial did not report this outcome (Lichstein 1985).

Discussion

Summary of main results

We analysed seven trials, which overall recruited 362 participants and included 264 of them in our analysis. Results of the main outcomes are synthesized in the 'Summary of findings' tables (Summary of findings table 1; Summary of findings table 2; Summary of findings table 3; Summary of findings table 4).

We aimed to assess the following groups of interventions: psycho-education and low-intensity psycho-educational intervention; cognitive therapy; behavioural therapy; psychodynamic psychotherapy and systemic therapy. We found no trials assessing psychodynamic therapy or systemic therapy.

The heterogeneity of the considered trials did not allow for a formal meta-analysis, and prompts caution in the interpretation; nevertheless, the results obtained let us to draw some conclusions.

The majority of the seven trials, which also are the most recent ones, propose psycho-educational interventions (Beheshtipoor 2015; Breakey 2014; Elander 2011; Mulders 2012), while the remaining three (and older) trials are about cognitive interventions (LaBaw 1975; Swirsky-Sacchetti 1986) and behavioral interventions (Lichstein 1985). These three trials, dating back more than 30 years ago, share the idea of relaxation as a central element of intervention, even if it is achieved by means of different techniques, and classified in this review as cognitive or behavioral interventions. The auto-hypnosis (self-hypnosis) techniques on the one hand (LaBaw 1975; Swirsky-Sacchetti 1986) and the relaxation techniques on the other (Lichstein 1985) are actually very similar, as Lichstein himself points out: “the autohypnosis training used by LaBaw resembled a self-control relaxation format” (Lichstein 1985, p. 151).

It should be noted that, nowadays, the distinction between cognitive interventions and behavioral interventions is no longer so clear-cut, and from the critical re-elaboration of these two models the Cognitive-Behavioral Approach was born.

Overall, the trials proposing psycho-educational interventions address all the primary outcomes expected in this review. Within this group of trials, from the results regarding mood and personal well-being, we are uncertain whether an intensive intervention based on computer-learning produces an increase in the sense of the self-efficacy in children and adolescents (Breakey 2014). This result is consistent with the Beheshtipoor trial on which, however, no meta-analysis was conducted due to the scarcity of data presented in the paper (Beheshtipoor 2015). On the contrary, when the intervention is aimed at adults aged 17 to 67 and based only on a 15- or 30-minute session, there is no evidence of its effectiveness in increasing participants' self-efficacy (Mulders 2012). It should be noted, however, that the method adopted in Mulders' trial is distorted by a bias in the questionnaire presentation, which implicitly induces all the respondents - even those randomly assigned to the control group - to place themselves on the high scores of the self-efficacy scale due to social desirability. This procedure, together with the limited number of participants, may have biased the study toward missing the effect of the intervention.

We found two trials investigating the effects of psycho-educational interventions on QoL, producing discordant results: the Breakey trial does not show any effect (very low-quality of evidence), while the Elander trial observes no difference in relation to the 'physical' health-related QoL, but an improvement of the 'mental' health-related QoL, but given this is low-certainty evidence, the results should be interpreted with caution (Breakey 2014; Elander 2011). Of note, was that the improvement especially occurs in participants with lower education levels.

Concerning coping, our analysis overall did not confirm the results presented by the authors of two of the included studies as far as increasing the disease-specific knowledge (Breakey 2014; Mulders 2012). Conversely, the effectiveness of one of the two interventions is confirmed with regard to increasing practical and self-management skills in adolescents (low-certainty evidence) (Breakey 2014,). A third trial differs from the previous ones because the DVD intervention targets only the motivational aspects that precede the pain-coping strategies and does not provide instruction for self-management skills or techniques (Elander 2011). The authors do not expect changes in the outcomes associated with self-management; on the contrary, they consider the effects on the pain coping strategies, pain acceptance and health-related QoL only in secondary analyses. The results indicate that the visual information (DVD) is only partially more effective than the written one because the DVD fruition could only reduce pre-contemplation and

negative thoughts about pain; however, no further effects are observed.

The evidence we retrieved with regard to cognitive interventions is limited (LaBaw 1975; Swirsky-Sacchetti 1986). The primary outcome reported in the Swirsky-Sacchetti trial is general distress (mood and personal well-being); however, as for this variable there is no comparison with the control group, the observed improvement may be due to a placebo effect or to the on-study effect more than to self-hypnosis (Swirsky-Sacchetti 1986).

No primary outcomes are assessed with regard to the behavioral intervention (Lichstein 1985).

Many trials referring to cognitive, behavioral and psycho-educational interventions assess changes for the secondary outcome of physical health in terms of pain reduction (Elander 2011; Lichstein 1985) or bleedings (measured by different strategies) (LaBaw 1975; Lichstein 1985; Swirsky-Sacchetti 1986). Our review is consistent with the original trials as published by the authors, and did not show any clear effect of the interventions on pain; only the study by LaBaw confirms a significant decrease in the bags of bloods used for participants using auto-hypnosis across the total period observed (30 months) (LaBaw 1975). The reduction was evident in the first two 10-months treatment period, but not anymore in the third period; this may be due to the experimental design adopted (small samples, length of the observation), or to a reduced effectiveness of auto-hypnosis over time. Although it was not possible to perform any meta-analysis on the Swirsky-Sacchetti trial about the use of hypnosis, it is worth noting that the results indicated by the author are in line with those by LaBaw (LaBaw 1975; Swirsky-Sacchetti 1986).

Overall completeness and applicability of evidence

Only seven trials eligible for inclusion in this review were identified. Such trials are homogeneous with regard to the socio-cultural context where they were carried out, as almost all of them were conducted in high-income countries (three in the USA, one in Canada, one in the UK and one in the Netherlands). Only one trial was carried out in a low-to-middle-income country (Iran). However, the included trials are heterogeneous in many other respects, including the focuses of the intervention (e.g. pain management, adherence to treatment, relaxation), the characteristics of the sample (age, number of participants involved), the outcome measures, the historical periods when they were conducted (from 1975 to 2015) and the levels of methodological rigor of the experimental design adopted, which limit the evidence of the results obtained.

For these reasons, it was not possible to combine the trials nor to conduct a meta-analysis, and as a consequence it is difficult to generalize the results. In regards to psycho-educational interventions in three trials (Beheshtipoor 2015; Breakey 2014; Mulders 2012), which seem to be promising for improving the disease-specific knowledge, self-efficacy and the practical self-management skills (especially if they are carried out during the developmental age), a greater effort is needed to set up more rigorous experimental designs and to appropriately communicate the data. The effectiveness of the intervention in improving self-efficacy and practical self-management skills of adolescents was confirmed only in the Breakey trial (very low-certainty evidence) (Breakey 2014). Moreover, the interventions aimed at increased relaxation capacity seem to be promising for reducing spontaneous bleedings (low- and very low-certainty evidence) (LaBaw 1975; Lichstein 1985; Swirsky-Sacchetti 1986), although the effectiveness could be confirmed only in the LaBaw trial (LaBaw 1975). However, the development of safe and effective pharmacological therapies (e.g. prophylaxis) has made the use of these techniques for reducing bleedings less relevant, at least in countries with high-income countries, while there is no trial conducted in low-to-middle-income countries that verifies the effectiveness of the relaxation techniques in those socio-cultural contexts. It should, however, be noted that two of these three trials do not take into account any of the review's pre-defined primary outcomes (LaBaw 1975; Lichstein 1985), while Swirsky-Sacchetti considers an indicator of 'Mood and Personal Well-being' (one of the review's primary outcomes) from a non-experimental perspective (Swirsky-Sacchetti 1986).

Overall, the RCTs included in this review cover a rather narrow field of intervention with respect to the psychological needs of individuals and the types of psychological support that we know to exist. Indeed, there are no trials on psychodynamic or systemic matrix interventions, which actually constitute a widespread segment of the psychotherapy universe. This is probably due to the fact that, by their very nature, these approaches are unlikely to lend themselves to experimental research designs to prove their effectiveness.

Finally, the few trials identified did not include interventions targeting other relevant issues of living with hemophilia, such as social inclusion or family adjustment. For example, to work on these issues a group situation is frequently used as a therapeutic tool (e.g. self-help groups or summer camps for children); while some of the interventions assessed in this review are carried out in groups, they do not use the group as the therapeutic factor.

Quality of the evidence

We judged the certainty of the evidence in this review to be low to very low (depending on the comparison and the outcome) due to issues of risk of bias, lack of applicability and imprecision (Summary of findings table 1; Summary of findings table 2; Summary of findings table 3; Summary of findings table 4).

A total of 362 participants were recruited and randomized and 264 participants were included in analysis within the seven trials. The sample size of included trials was mostly small, between seven and 196 participants

recruited and between seven and 108 analysed. Some of the trials recruited only specific ages (e.g. only children, only adolescents or only adults), therefore, results for some comparisons and interventions may not be generalisable to wider populations.

All of the seven trials had methodological inadequacies or did not report clear information regarding their designs and therefore may be at risk of bias. None of these trials blinded participants or clinicians, since blinding would have been difficult or impossible due to the nature of the interventions. However, none of the trials stated whether outcome assessors were blinded, therefore, all of the trials may be at risk of detection bias. Also, three of the trials excluded between 30% to 56% of randomized participants from analyses (due to loss to follow-up and other reasons, see Risk of bias in included studies), introducing bias due to incomplete outcome data.

Furthermore, some of the trials did not report specific or numerical results relating to the outcomes of the review (rather the trials made only a statement of no difference between groups), and in several instances, post-treatment results were reported only for the intervention groups (e.g. improvement from baseline) but no post-treatment results were reported in control groups to allow a between-group comparison. Without any measures of change in the control groups, it is difficult to judge the clinical significance of any differences within the intervention groups.

Potential biases in the review process

A rigorous methodological approach in line with Cochrane MECIR standards (MECIR 2012) was applied to the review and a comprehensive search strategy was employed as outlined above (Electronic searches), therefore, we do not believe that our methodological approach has introduced any bias into the review.

Due to the heterogeneity of design, intervention, control and trial-defined definitions of broad outcomes of interest to review, it was not possible or appropriate to include all trials in the meta-analysis. In many instances, we felt it would be more appropriate to summarise results narratively or perform separate analyses where outcome definitions were too different to be combined (e.g. measures of coping or physical health).

Agreements and disagreements with other studies or reviews

Concerning the ability of people with hemophilia to modify skills and health related behaviors, our results, though limited to the very few RCTs, are partially in line with traditional reviews showing that psycho-educational interventions can improve such outcomes (Deakin 2005; Sansom-Daly 2012; Savage 2014). Based on our results, one can reaffirm the general principle that knowledge gained from an educational intervention is unlikely to be translated into changes in behavior if participants are not engaged for a sufficient amount of time through active learning techniques (Nation 2003; Savage 2014; Small 2009).

Despite other Cochrane Reviews related to cystic fibrosis (Savage 2014) and epilepsy (Bradley 2008; Shaw 2007; Stokes 2007), and a systematic review on psychological interventions for adolescents and young adults living with chronic illness (Sansom-Daly 2012), having shown that psycho-educational interventions aimed to improve self-management skills are able to improve disease-specific knowledge of participants, our review did not confirm this relation for hemophilia (Beheshtipoor 2015; Breakey 2014; Mulders 2012). It has to be noted that not all the trials on this type of interventions have used knowledge as an outcome (Beheshtipoor 2015) or have made available data for analysis in the format required for this review (Mulders 2012).

There are only two trials included in this review that have reported QoL as an outcome and both involve psycho-educational interventions aimed at increasing the participants' self-management skills. Previous systematic reviews have shown a good capacity for this type of intervention in improving the QoL of chronically ill individuals (Effing 2007; Gibson 2002), one has given more discordant results (Sansom-Daly 2012), while the last has not been able to perform meta-analysis (Savage 2014). In the present review, the only evidence is related to the work by Elander which achieves an improvement in the mental domain of QoL (Elander 2011).

Finally, our results showing a possible effect of relaxation and self-hypnosis techniques in reducing the frequency of bleeding (LaBaw 1975) are in line with other Cochrane Reviews that have highlighted that similar techniques can produce significant improvements on physical health outcomes in children and adults with asthma, such as asthma symptoms and lung function (Yorke 2005; Yorke 2006).

Authors' conclusions

Implications for practice

We aimed to provide a structured summary of the psychological interventions that have been tested in the field of hemophilia. The evidence we found was limited, however, there are a few findings that are relevant to clinical practice.

Given the low certainty of the evidence, we are uncertain whether the psycho-educational interventions are useful in promoting a sense of self-efficacy and better self-management skills when aimed at young people (children and adolescents). No evidence of effects were detected in the only trial testing the intervention in adults. The lifestyle and habits that individuals build up to manage the illness, as well as the beliefs about their self-efficacy, are aspects that develop and settle during life and are thus more difficult to modify in adulthood.

In this review, hypnosis was considered as a cognitive intervention. However, hypnotic induction for therapeutic purposes is a technique that has been used within different theoretical frameworks in history. This would not change the evaluation of the trials and their results deserve a specific consideration. Indeed, the interventions based on the auto-hypnosis (self-hypnosis) (LaBaw 1975; Swirsky-Sacchetti 1986) and similar relaxation techniques (Lichstein 1985) were conducted in the 1970s and 1980s and showed promising results in reducing the burden of bleeding. These studies have been abandoned, most likely because of the introduction of new effective drug therapies, which therefore made the use of psychological interventions aimed at improving the physical health of individuals obsolete. From a practical view point, however, since over 80% of the hemophilia population does not have access to treatment, these cognitive-behavioral techniques, in their most current and advanced form, could be providing suboptimal care but still valuable relief from symptoms.

As a final observation, it is worth noting that from this review it is difficult to understand whether there is a relationship between the professional competences of the person providing the intervention and the evidence produced. In fact, only LaBaw and Lichstein specify that their interventions were conducted by a therapist and by an advanced graduate student in clinical psychology respectively (LaBaw 1975; Lichstein 1985).

All four psycho-educational interventions were delivered through technologies (DVD and computer) and self-administered. In conducting a review on the effectiveness of such interventions, it becomes therefore relevant to understand the contribution of psychology (in terms of both theoretical paradigms and professional knowledge) in the design of these educational tools and their contents. Unfortunately, this argument is not always explicitly discussed by the authors of the trials and therefore, from the available documentation, we can say that only two of the four interventions evaluated (Beheshtipoor 2015; Elander 2011) seem to have benefited from some contribution of psychologists in the definition of the intervention device. In the case of psycho-educational interventions that are not based on the direct interaction with a professional but on the autonomous use of pre-established devices and platforms, it would be desirable for these to be devised by multi-disciplinary teams where the psychologist can contribute at the very least as expert in communication and learning processes.

Implications for research

The major problem we encountered in this review is the heterogeneity of study designs, interventions and outcome measured used across the studies. We strongly recommend that researchers in the field consider developing a core outcome set to streamline future research (Kirkham 2017). While there is no core outcome set, the main outcome measures we have identified in this review may constitute a solid starting point for harmonizing research efforts.

The results we have found on the effects of psycho-educational interventions on children and adolescents and of behavioural and cognitive interventions based on the induction of states of relaxation, are promising enough to suggest expanding the testing of such interventions in the future in order to acquire more evidence. Low-intensity psycho-education interventions with adults are more likely to produce changes (at least in the short term) on the cognitive dimensions, such as the disease knowledge and the mastery of practical skills (e.g. self-injection), as suggested by Mulders (Mulders 2012).

On this note, we think is important to point out that while in other fields of hemophilia there has been resistance and reluctance to perform randomized controlled trials, this does not seem the case in the field of psychological interventions. No harm has been reported, and individuals with hemophilia have willingly taken part in the trials. The outcome measures that proved to be of value to assess psychological interventions in our review are reported by individuals with hemophilia, and some form of blinding for outcome assessors should be recommended. Similarly, an active control for those who do not undergo the treatment being studied should be put in place.

The role of potentially relevant variables in modifying the impact of the intervention (mediating or moderating variables) should be controlled for and assessed. For example, the severity of hemophilia or the perception of its impact in everyday life can modify the individual's expectations or compliance towards the psychological intervention.

Moreover, many of the trials we observed were performed with the involvement of researchers with different expertise and background, as expected in a borderline area like this. We suggest continuing along this direction.

In our clinical experience some people with hemophilia (or their parents when children) are offered psychological interventions through their hemophilia treatment centers or through patient associations. Some of these interventions are described in the literature (Dunne 1991; Omura 2013; Parsons 2000; Penica 2008; Slifer 2009), even if they do not report evidence through randomized controlled trials. It would be interesting to undertake a review of the observational evidence with the aim of mapping the different available interventions and their stage of development. Such a review would not inform clinical practice, but would certainly help in planning multicenter clinical studies.

Acknowledgements

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group. The views and opinions expressed therein are those

of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

Contributions of authors

Laura Palareti: co-ordination of the project at the review stage, search strategy development, undertaking searches and retrieving papers for the review, screening retrieved papers against the inclusion criteria, writing to authors of papers for additional information, extracting data from included papers, appraising quality of papers, data analysis and interpretation, data management for the review, entering data into RevMan, interpretation of data analysis, writing the review and approving its final version.

Giannino Melotti: undertaking searches and retrieving papers for the review, screening retrieved papers against the inclusion criteria, extracting data from included papers, appraising quality of papers, data management for the review, entering data into RevMan, interpretation of data analysis, writing the review and approving its final version.

Frederica Cassis: conception and design of the review, coordinating the project at the protocol stage, writing the review protocol, search strategy development, undertaking searches and retrieving papers for the review, screening retrieved papers against the inclusion criteria, writing to authors of papers for additional information.

Alfonso Iorio: conception and design of the review, writing the protocol, search strategy development, adjudicating eligibility and data extraction, providing general advice on the review and interpretation of results, drafting the review and approving its final version.

Sarah Nevitt: writing to authors of papers for additional information, data analysis and interpretation, data management for the review, entering data into RevMan, writing the review and approving its final version.

Declarations of interest

Laura Palareti: none known.

Giannino Melotti: none known.

Frederica Cassis: I am a member of the International Advisory Board of the Hemophilia Experiences Results and Opportunities Project (HERO) sponsored by Novo Nordisk International, 2011. I have given paid presentations occasionally as a health consultant on psychosocial aspects in hemophilia. I am also a member of the psychosocial committee of the World Federation of Hemophilia (WFH) and a volunteer for workshops on psycho-education in hemophilia.

Sarah Nevitt: none known.

Alfonso Iorio: I do not perceive any relevant conflict of interest for the above disclosures as far as the matter of this review is concerned. There is no drug involved in this review, and the Hemophilia Expectations Resources and Opportunities Project (HERO) is a NovoNordisk funded project with an independent international advisory board aiming at investigating psychosocial aspects of hemophilia, and raising awareness on the topic.

Differences between protocol and review

We edited the 'Types of studies' to be included to clarify that only randomized studies would be included.

We edited the definition of the primary outcome of 'Mood' to 'Mood and personal well-being' which provides a more appropriate measure of the efficacy of the interventions.

We edited the definition of the secondary outcome 'Compliance' to reflect both compliance to prophylaxis treatment and to the trial intervention.

We edited the definition of the secondary outcome 'Physical health' to include pain intensity as a sub-domain of this outcome.

In a post hoc change from the protocol, we have presented four summary of findings tables, one for each comparison of the review (Summary of findings table 1; Summary of findings table 2; Summary of findings table 3; Summary of findings table 4).

Published notes

Characteristics of studies

Characteristics of included studies

Beheshtipoor 2015

Methods	Parallel group trial
Participants	Participants attended the hemophilia ward of Shahid Dastgheib Hospital, affiliated to Shiraz University of Medical Sciences, Shiraz, southern Iran during 2014 N = 40 37 males and 3 females (all females were included in experimental group) Aged 8 - 12 years Experimental group = 20 participants. Mean (SD) age: 10.69 (1.2) years Control group = 20 participants. Mean (SD) age: 10.50 (1.3) years
Interventions	Computer-based learning hemo-action games Follow-up after 2 months
Outcomes	Self-efficacy - only the 17 items of the General Self Efficacy subscale (Sherer 1982)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The authors stated: "Based on blocking randomization method 20 patients were placed in each case and control group." (Beheshtipoor 2015, p. 150)
Allocation concealment (selection bias)	Unclear risk	The authors stated: "Following the eligibility assessment, the patients were familiarized with the study and enrolled." (Beheshtipoor 2015, p. 150)
Blinding of participants (performance bias)	High risk	Participants were not blinded
Blinding of personnel (performance bias)	Unclear risk	Not openly stated
Blinding of outcome assessment (detection bias)	Unclear risk	Not openly stated
Incomplete outcome data (attrition bias)	Low risk	All participants entering trial
Selective reporting (reporting bias)	High risk	We have not been able to access to the trial protocol. Statistical data about comparisons between groups over the time are missing. All mean scores are provided, but some SDs are missing. Some results are reported only in the abstract
Other bias	Unclear risk	It is unclear whether more than 40 participants were eligible and it is unclear how the enrolment was managed. The trial author could not be contacted to clarify (risk of bias not for the group assignment but for the general selection of participants)

Breakey 2014

Methods	Parallel-group trial
Participants	Participants attended the Hospital for Sick Children, Toronto, McMaster Children's Hospital, Hamilton and CHU Ste. Justine, Montreal 39 participants were randomized, 29 received allocated intervention (baseline) and only 17 completed the program and than were analysed Sample characteristics were provided only for the 29 participants who received allocated intervention (baseline). N = 29 (18 hemophilia A, 9 hemophilia B, 2 did not know their hemophilia type) Aged 13 - 18 years All males. Mean (SD) age: 15.9 (1.34) years Experimental group = 16 participants. Mean (SD) age: 16 (1.44) years Control group = 13 participants. Mean (SD) age: 16.1 (1.44) years The authors stated: "There was no statistical differences in the demographics of the study groups with or without the drops outs included (P = 0.47)." (Breakey 2014, p. 788)
Interventions	Internet-based self-management and transitional care program for youth with hemophilia The intervention is an 8-module program that consists of haemophilia-specific information, self-management strategies and social support and is available in English and French (29,000 + words total, 80 pages of content) The content is interactive, including 8 videos (3:05 - 6:07 min each), animations, illustrations and knowledge quizzes Adolescents were asked to log on to the site at least once per week to complete a module that was designed to take between 20 and 30 min, with the goal of completing the program in 8 - 10 weeks During the study period, the intervention group was contacted weekly by a coach
Outcomes	**Primary outcomes** HRQL-Canadian Haemophilia Outcomes-Kids' Life Assessment Tool (CHOK-LAT) (35 items) Self-Efficacy-Sherer Scale (GSE-S 12) (12 items) Self-Manageent-Skills Assessment Guide (21 items about adolescents' perceived medical self-management abilities and readiness for transition) Disease-specific knowledge (20 items) Program satisfaction (11 items) **Evaluation at**: baseline; post program "Participants took a range of 10-26 weeks to complete the program, with an average completion time of 14 +/- 5 weeks." (Breakey 2014, p. 788)
Notes	Only 17 participants out of 39 randomized who completed the trial were analysed

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors stated: "Following enrolment, the adolescents were randomized to either the intervention or control arm. A fixed allocation randomization scheme used blocked randomization with blocks of four participants assigned to the two groups in each of the three study centres. An online random number generator was used for the randomization. Group assignments were identified by ID number and revealed to the adolescents after completion of the baseline measures." (Breakey 2014, p. 786)
Allocation concealment (selection bias)	Unclear risk	Not specified if the association between the ID number and group was defined before or after the procedure
Blinding of participants (performance bias)	High risk	Not blinded
Blinding of personnel (performance bias)	Unclear risk	Not openly stated
Blinding of outcome assessment (detection bias)	Unclear risk	Not openly stated
Incomplete outcome data (attrition bias)	High risk	39 adolescents were randomized, 29 completed baseline measures and only 17 were analysed (11 intervention group and 6 control group). 22 randomized participants were lost (56.41%)
Selective reporting (reporting bias)	Low risk	The outcomes reported are congruent with the protocol
Other bias	Low risk	No other bias identified

Elander 2011

Methods	Parallel-group trial
Participants	Participant recruitment was through the membership and registration list of the Haemophilia Society UK. Taken baseline data n = 196 (Mean (SD) age = 49.3 (12.7) years, range 20 - 84 years) Experimental group = 97 participants, control group = 99 participants Analyzed 108 participants, experimental group = 57, control group = 51 All males Hemophilia A or B / any severity
Interventions	A DVD (digital video disk) plus booklet intervention to increase readiness to self-manage joint pain secondary to hemophilia Follow-up after 6 months
Outcomes	Readiness to self-manage pain, measured by the 4 scales of the PSOCQ Pain coping Pain acceptance Health-related QoL (RAND-36) How often participants used material (DVD and booklet) How helpful participants found material (DVD and booklet)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The authors stated: "A computer-generated random sequence of 0s and 1s, with equal numbers of 0s and 1s within each block of 10, was used to allocate those enrolled to 1 of 2 mailings: the DVD plus booklet, or booklet only. Blind allocation was achieved by assigning each participant a study number in a sequence from 1 to 196. Those numbers, separated from all identifying information about participants, were then sorted into a random sequence and merged with the computer-generated sequence to determine which individuals received which mailing." (Elander 2011, p. 2334)
Allocation concealment (selection bias)	Low risk	The authors stated: "The procedure for recruitment and data collection preserved the anonymity of participants, who were identified only by a number assigned specifically for the study. The Haemophilia Society retained all information about the identity and contact details of participants, and mailings to deliver the booklet/DVD and collect study data were undertaken by the Society. Baseline data were collected before the DVD and/or booklet were mailed, and only those who returned baseline questionnaires were enrolled in the trial. After the 6-month follow-up, the DVD was sent to all those who previously received only the booklet." (Elander 2011, p. 2334)
Blinding of participants (performance bias)	High risk	Not blinded
Blinding of personnel (performance bias)	Unclear risk	Not openly stated
Blinding of outcome assessment (detection bias)	Unclear risk	Not openly stated
Incomplete outcome data (attrition bias)	High risk	44.9% of randomized participants were not analyzed (60 lost + 28 missing data)
Selective reporting (reporting bias)	Unclear risk	We haven't been able to access to the trial protocol. A case of selective reporting is more evident in the secondary study reported in the further paper of Stalker & Elander (2015), as the outcome "readiness to self-manage pain" who was the primary outcome in the first publication is dropped without any justification
Other bias	Low risk	No other bias identified

LaBaw 1975

Methods	Parallel-group trial
Participants	Participants assemble in the normally illuminated auditorium of the Psychiatric Clinic at the University of Colorado Medical Center 20 participants aged between 5 and 48 years, 10 experimental group (aged 6 - 33 years) and 10 control group (aged 5 - 48 years) All males
Interventions	Auto-hypnosis (self-hypnosis) intervention (trance therapy), 1 hour, twice each month over a period of 40 months
Outcomes	Blood use (bags of blood. 90 AHF each)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The author only says that the participants were randomized
Allocation concealment (selection bias)	Unclear risk	Not mentioned by the author
Blinding of participants (performance bias)	High risk	Not blinded
Blinding of personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	The authors stated that the results were evaluated by an independent statistician, but they did not specify if he was blinded
Incomplete outcome data (attrition bias)	Low risk	All participants entering trial
Selective reporting (reporting bias)	Unclear risk	The protocol is not available Considering the stated aims of the paper the outcomes are all reported but from the introduction there is the doubt that they have collected other measures, e.g. "spontaneous fibrinolysis associated with the specific anxieties of surgery and trauma as also been recorded"
Other bias	Low risk	No other bias identified

Lichstein 1985

Methods	Combined multiple-baseline, partial-cross-over design
Participants	Indiviudals with hemophilia in the Memphis area 7 participants (mean age (years) = 32.6) 2 participants received self-control relaxation (Group A) 2 participants received progressive relaxation (Group B) 3 participants received no treatment (Group C)
Interventions	Progressive relaxation vs self-control relaxation vs no intervention (delayed) "Patients were instructed to practice their relaxation technique (progressive or self-control) daily in the interim between sessions and during a 2-month post-treatment period" Follow-up after 2 months
Outcomes	Bleeding frequency Factor use (concentrate consumption) Daily tension rating (0 = no tension experienced, 5 = tension ruined the whole day) Arthritic pain rating (rated the highest degree of arthritic pain experienced each day on scale 0-5. Scale adapted from Budzynski 1973) Bleeding pain rating (rated the highest degree of bleeding pain experienced in each episode on scale 0-5. Scale adapted from Budzynski 1973)
Notes	The trial had a partial cross-over design; after 2 months of treatment, all participants crossed over onto the most effective treatment (self-control relaxation) and continued to be followed up. Results presented below apply only to the first 2 months of the trial, prior to cross-over

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Allocation method is not mentioned by the authors
Allocation concealment (selection bias)	Unclear risk	Concealment is not mentioned
Blinding of participants (performance bias)	High risk	Not blinded
Blinding of personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Not openly stated
Incomplete outcome data (attrition bias)	Low risk	All participants entering trial
Selective reporting (reporting bias)	Unclear risk	The protocol is not available
Other bias	Low risk	No other bias identified

Mulders 2012

Methods	Randomized controlled intervention trial with a pre-test/post-test design
Participants	Individuals on home treatment were recruited from the Haemophilia Treatment Center at the Erasmus Rotterdam, The Netherlands 30 participants, median age = 34 years (range 16 - 67 years), all males. 16 intervention group, 14 control group 23 participants had hemophilia A and 7 had hemophilia B 60% of the participants had severe haemophilia 12 of the 30 participants are on prophylaxis two or three times a week, 8 participants were treated or prophylaxis in the past, but were on demand therapy at time of inclusion in the trial Participants in the intervention group are younger and more live with family
Interventions	"The e-learning program, a didactic instrument with a central role for information and interaction via technology, has been chosen as an intervention. The program is based on the instruction book in hor patients with haemophilia, developed by the Dutch Society for Haemophilia Nurses. The e-learning pr about 15 - 30 min and is an interactive multimedia programme based on the Moodle open source lea environment (www.moodle.org). version in Dutch is available on www.learn2grow.nl/emc (login code: erasmus2011)." (Mulders 2012, p. 695). Follow-up after 1 month
Outcomes	Competence to manage the disease (knowledge) Self-efficacy Practical skills checklist
Notes	The instruction given to fill in the self-efficacy scale introduces a social desirability bias in the respor haemophilia patients treating themselves at home score high in this, as far as specialised literature re some questions to verify this claim." (retrieved from: https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fj.1365-2516.2012.02). This instruction may not be responsible for erroneous results in the comparison between the interver as all are in home treatment, but it's likely to generate a general increase in the scores to meet the re desirability)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to following to the e-learning group or to the control group by pulling a sealed envelope
Allocation concealment (selection bias)	Low risk	Participants were randomized after pre-test assessment, by pulling a sealed envelope that assigned to an e-learning program or to no intervention
Blinding of participants (performance bias)	High risk	Not blinded
Blinding of personnel (performance bias)	Unclear risk	Not stated
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	All participants entering trial
Selective reporting (reporting bias)	Unclear risk	The protocol is not available
Other bias	Low risk	No other bias identified

Swirsky-Sacchetti 1986

Methods	Pre test- post-test design
Participants	The sample consisted of 30 people with hemophilia on home therapy under the auspice of the Cardeza Foundation Hemophilia Center of Jefferson Medical College. All are males. Aged 11 - 50 years (mean age = 30 years). Normally distributed on socio-economic and educational variables Randomized 30 participants: 16 intervention group, 14 control group Analyzed 24 participants: 13 intervention group, 11 control group 2 treatment and 1 control participant had inhibitor and therefore were excluded from those statistical analysis which involved magnitude of factor usage
Interventions	Self-hypnosis "The treatment group received a comprehensive 6-week training program including support, education, deep relaxation, and self-hypnosis." (Swirsky-Sacchetti 1986 , p.71) Training session: "The training was held in small groups of three to four members based upon Ss (study subjects) time preferences, with the exception of the two 11-year-olds, who were assigned to one group so that the training could be directed at their developmental level. The groups met for 6 consecutive weekly sessions, each 75-90 minutes long. The Ss were told that the effectiveness of the training relied heavily upon practice, and that they should use the information presented and experiment with self-hypnosis techniques in their daily lives." (Swirsky-Sacchetti 1986 , p.75) Self-hypnosis session: "Self-hypnosis was taught in a gradual fashion. Initially, Ss were given a cassette tape with an induction, including suggestive communications for decreased bleeding, ego-strengthening, deep muscle relaxation, and sensations of floating. The Ss were encouraged to listen to the tape at least once daily but also to develop their own most effective individualized inductions. Each group session began with varied group induction techniques, images, and suggestions. Rapid (1-2 minute) inductions were taught as a tool for combating stressful experiences during the day as they occurred." (Swirsky-Sacchetti 1986 , p. 76) Follow-up at 18 weeks
Outcomes	Factor usage (units/kg/month) (intervention group and control group) General distress level (SCL-90) (intervention group only)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The authors stated: "All Ss (study subjects (N = 30) volunteered to participate in the project and were randomly assigned by a coin-flipping method to either a treatment (N = 16) or a waiting list control (N = 14) group." (Swirsky-Sacchetti 1986, p. 74)
Allocation concealment (selection bias)	Low risk	The authors stated: "All Ss (N = 30) volunteered to participate in the project and were randomly assigned by a coin-flipping method to either a treatment (N = 16) or a waiting list control (N = 14) group. ... The control Ss received a letter explaining that, for purposes of scientific research, they would receive the same training as the treatment group after the initial follow-up period. During this waiting period, the control group received the standard comprehensive care of the home therapy regimen, including regular physician visits or social work assistance as needed, but they did not receive any group instruction." (Swirsky-Sacchetti 1986, p. 74 - 5)
Blinding of participants (performance bias)	High risk	Not blinded
Blinding of personnel (performance bias)	Unclear risk	Not specified
Blinding of outcome assessment (detection bias)	Unclear risk	Not specified
Incomplete outcome data (attrition bias)	High risk	30% of attrition: 3 from the experimental group plus 3 from the control group dropped out. Moreover, 2 from the experimental group plus 1 from the control group developed inhibitors and were excluded from the assessment of factor usage
Selective reporting (reporting bias)	Unclear risk	The protocol is not available
Other bias	Low risk	No other bias identified

Footnotes

AHF: antihemophilic factor
CHOKLAT: Canadian Haemophilia Outcomes - Kids' Life Assessment Tool
GSE-S: Generalized Self-Efficacy - Sherer Scale
HRQL: health-related quality of life
PSOCQ: Pain Stages of Change Questionnaire
QoL: quality of life
RAND: Research and Development (corporation)
SCL-90: Symptom Checklist 90
SD: standard deviation

Characteristics of excluded studies

Beheshtipoor 2012

Reason for exclusion	Pre- and post- analyses performed on a single group

Cuesta-Barriuso 2014

Reason for exclusion	Not a RCT

Cuesta-Barriuso 2018

Reason for exclusion	The intervention is not of a psychological nature

Dunne 1991

Reason for exclusion	Pre- and post- analyses performed on a single group

Firoozabadi 2012

Reason for exclusion	The intervention is not of a psychological nature

Heydari 2018

Reason for exclusion	Not a RCT

ISRCTN63283043

Reason for exclusion	Intervention targeted are nurses and not people with hemophilia

Kang 2012

Reason for exclusion	Intervention targeted only mothers of children with hemophilia not people with hemophilia

Magli-Barioz 2004

Reason for exclusion	Pre- and post- analyses performed on a single group

NCT02198014

Reason for exclusion	The intervention is not of a psychological nature

NCT02825706

Reason for exclusion	The intervention is not of a psychological nature

NCT03136003

Reason for exclusion	The intervention is not of psychological nature

Omura 2013

Reason for exclusion	Not a RCT

Parsons 2000

Reason for exclusion	Not a RCT

Penica 2008

Reason for exclusion	Single-case study

Sergis-Deavenport 1983

Reason for exclusion	Not a RCT

Slifer 2009

Reason for exclusion	RCT on chronic illness where the only 2 people with hamophilia were in the same group

Thomas 2001

Reason for exclusion	Only a descriptive paper

Von Mackensen 2012

Reason for exclusion	the intervention is purely of a physiotherapeutic nature, therefore It doesn't match the inclusion criteria

Walker 2004

Reason for exclusion	the intervention is not of psychological nature, as it is based on the use of computer instead of paper diaries; therefore It doesn't match the inclusion criteria

Wincott 1976

Reason for exclusion	A descriptive paper about psychosocial aspects of hemophilia. It lists different types of interventions to enact a comprehensive approach, but no trials are reported

Footnotes

RCT: randomized controlled trial

Characteristics of studies awaiting classification

Kang 2005

Methods	Quasi-experimental design
Participants	40 young adults with hemophilia (21 in the experimental group and 19 in the control group)
Interventions	Self-help group program for young adults
Outcomes	self-efficacy, QoL, depression
Notes	Full text awaiting translation

Karimi 2014

Methods	RCT
Participants	50 individuals with severe hemophilia A
Interventions	Logothraphy
Outcomes	Self-concept
Notes	Abstract only. Await full report

Footnotes

QoL: quality of life
RCT: randomized controlled trial

Characteristics of ongoing studies

IRCT201502079267N4

Study name	The effect of psychological empowerment on psychological outcome in hemophiliac adolescents
Methods	Randomized, single blinded, parallel design
Participants	Males and females aged between 13 - 19 years, with hemophilia, hereditary factor VIII deficiency, hereditary factor IX deficiency. Target sample size: 60
Interventions	Control group does not receive any intervention but they are monitored for comparing with the intervention group Intervention 1: Intervention group will attend in 8 sessions of psychological empowerment. Psychological empowerment interventions are a group of interventions, including awareness among the participants about the nature of the disease, hemophilia and its symptoms, strategies for problem-solving skills and strategies to reduce stress, depression and anxiety. Intervention 2: Control group does not receive any intervention but they are monitored for comparing with the intervention group Intervention group will attend in 8 sessions of psychological empowerment. Psychological empowerment interventions are a group of interventions, including awareness among the patients about the nature of the disease, hemophilia and its symptoms, strategies for problem-solving skills and strategies to reduce stress, depression and anxiety. Rehabilitation
Outcomes	Primary outcomes: coping mechanisms. Time point: immediately and 1 month after the intervention. Method of measurement: Lazarus Questionnaire Secondary outcomes: anxiety, stress and depression. Time point: immediately and 1 month after the intervention. Method of measurement: DOSS- 21 Questionnaire
Starting date	20 February 2015
Contact information	Giti Setoodeh (setoodeh@sums.ac.ir)
Notes	

IRCT20180311039037N1

Study name	Effect of Benson relaxation on hemophilia disease
Methods	Randomized, not blinded, parallel design. Participants divided into 2 experimental and control groups by random block method
Participants	Males and females (18 years or older) with hemophilia type A, (deficiency factor 8), hemophilia type B (deficiency factor 9)
Interventions	Intervention 1: the test group is placed under the Benson relaxation technique. Control group received routine care. After the intervention, if the relaxation technique is effective, the intervention for the control group is also performed and the instructional CD is given to this group
Outcomes	Primary outcome(s): • acceptance of pain involves feeling the tendency to have or experience some of the events. Time point: before the intervention and 3 days after the end of the intervention. Method of measurement: chronic pain acceptance questionnaire. • belief of pain are thoughts that the individual believes to be correct and legitimate. Timepoint: before the intervention and 3 days after the end of the intervention. Method of measurement: Strogan's pain belief check list. • Severity of pain. Time point: before the intervention and 3 days after the end of the intervention. Method of measurement: pain severity scale, NRS
Starting date	07 October 2018
Contact information	Madineh Alizadeh (m.alizadeh4583@gmail.com)
Notes	

NCT03529474

Study name	Psychology and Physiotherapy Approach of Chronic Pain in Patients With Hemophilia
Methods	Interventional (clinical trial). Parallel assignment. Double-blinded (investigator and outcome assessor) The purpose of this study is to improve the perception of the experience of chronic pain, as well as functionality and quality of life in hemophilic patients with chronic pain Secondary objectives are: • to change the perception that the patient has of their pain, to improve the coping strategies and to increase the perception of self-efficacy of patients in pain management • to increase the resources that allow a better self-regulatory of emotional, cognitive and competential of the pain experience, reverting in the emotional state of patients, particularly in levels of anxiety and depression • to improve functional capacity and musculoskeletal status • to improve quality of life • to determine whether changes / improvements are maintained over time 3 months after finishing the program

Participants	19 participants enrolled. Inclusion criteria: • diagnosis of haemophilia A or B • age between 18 and 60 years • informed consent signed. • signs of arthropathy according to clinical criteria (score Gilbert) and / or radiological criteria (score Pettersson) in at least one of the 6 joints most commonly affected (ankles, knees or elbows) • chronic pain defined as persistent pain lasting at least six months and resistant to conventional medical therapy. It differs from the acute pain not only in its longer duration, but also sometimes persists even after the cause that produced it has disappeared. • Absence of active coping strategies, understanding the concept of coping as those cognitive and behavioral efforts made by the individual in order to manage internal and external demands generated by their chronic pain condition and that involve a challenge to their potential individual resources Exclusion criteria: • presence of inhibitor to FVIII or FIX • another haemostatic defect • patients with severe cognitive deficits with which it is not possible a cognitive psychological intervention • the inability to attend physiotherapy sessions for 12 consecutive weeks (7 supervised and 31 self-monitored) • surgical procedures performed 6 weeks prior or during the intervention protocol • not acceptance or withdrawal of informed consent
Interventions	Treatment group: psychology and physiotherapy group Psychological program consists of 4 sessions, 2 hours each, 4 months • Psychoeducation. Influence of psychological factors on chronic pain: modulators of pain experience. Biopsychosocial model of pain. • Training techniques of psychological management of pain: diaphragmatic breathing and progressive muscle relaxation to control vicious circle pain-tension-pain. • Kinesiophobia. Rational regulation of the activity level: cognitive therapy (management of irrational believes about pain) and organisation of time and reinforcement activities. Physiotherapy program consists of 3 domiciliary sessions per week (including physical exercise and stretching), 1 hour per session, 4 months: • aerobic exercise:walking, cycling • warm-up: active ROM exercises of ISE • progressive resistance training with elastic bands of ISE • stretching of ISE Placebo comparator: control group Control group: normal daily activities usual daily activities

Outcomes	Primary outcomes (Time frame: baseline, 4 months, 7 months) 1. Changes in perceived self-efficacy: Chronic Pain Self-Efficacy Scale Spainsh Version. (Martín-Aragon 1999). The scale contain 3 subscales: self-efficacy in the control of symptoms; self-efficacy in physical functioning, and self-efficacy in pain management. Secondary outcomes (Time frame: baseline, 4 months, 7 months) 1. QoL related with health 2. Emotional status (time frame: baseline, 4 months, 7 months) 3. Nociceptive pain (time frame: baseline, 4 months, 7 months) 4. Neuropathic pain (time frame: baseline, 4 months, 7 months) 5. Kinesiophobia 6. Functional capacity: the timed "Up & Go" test 7. Functional capacity: the Sit-to-stand test 8. Functional capacity: 2-min walk test 9. Self-perceived functional capacity 10. Active range of movement 11. Joint health status
Starting date	18 May 2018
Contact information	Principal Investigator: María García Dasí, Psych Instituto de Investigación Sanitaria La Fe. Hospital Universitari i Politècnic La Fe
Notes	Sponsors and collaborators • Instituto de Investigacion Sanitaria La Fe • Pfizer

Pinto 2016

Study name	Effectiveness of Psychological Interventions in Haemophilia (PSY_HaEMOPEQ)
Methods	Parallel RCT
Participants	66 adult males with mild or severe hemophilia randomized in 3 groups
Interventions	CBT vs hypnosis, vs no intervention
Outcomes	Pain management and prevention, emotional state regulation, QoL
Starting date	November 2016
Contact information	Patrícia Ribeiro Pinto, PhD, University of Minho
Notes	

Footnotes

CBT: cognitive-behavioural therapy
HAL: haemophilia activities list
HJHS: hemophilia joint health score
NGS: Numerical Grading Scale
QoL: quality of life
RCT: randomized controlled trial
ROM: range of motion
VAS: visual analog scale

Summary of findings tables

1 Summary of findings – DVD plus information booklet compared to information booklet alone for hemophilia

DVD plus information booklet compared to information booklet alone for hemophilia						
Patient or population: adults and children with hemophilia **Settings**: outpatients **Intervention**: DVD plus information booklet self administered **Comparison**: information booklet alone						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Information booklet alone	**DVD plus information booklet**				
Mood or personal well-being Follow-up: NA	Outcome not reported				NA	
Coping strategies: Pain Stages of Change Questionaire, Haemophilia Pain Coping Questionnaire, Chronic Pain Acceptance Questionnaire Follow-up: 6 months	Participants who received the booklet plus the DVD may have lower pre-contemplation scores and negative thoughts than those who received only the booklet There may be little or no difference between groups in terms of contemplation, action or maintenance, active coping, passive adherence, activity engagement or pain willingness		NA	108 (1 study)	⊕⊕⊖⊖ **low**[a,b]	
QoL: Rand36a questionnaire Follow-up: 6 months	Participants who received the booklet plus the DVD may have higher scores in the mental health domain than those who received only the booklet There may be little or no difference between groups in the physical health domain		NA	108 (1 study)	⊕⊕⊖⊖ **low**[a,b]	
Compliance or adherence to the trial intervention (including satisfaction): use of intervention at least once Follow-up: 6 months	725 per 1000	740 per 1000 (587 to 928 per 1000)	**RR 1.02** (95% CI 0.81 to 1.28)	108 (1 study)	⊕⊕⊖⊖ **low**[a,b]	The 57% of those who received the DVD and 66% of those who watched it at least once, rated it as helpful

Physical health: pain intensity (VAS post-treatment scores) Follow-up: 6 months	The mean VAS score post-treatment was 5.33 in the information booklet alone group	The mean VAS score post-treatment was 0.28 lower (1.27 lower to 0.71 higher) in the DVD plus information booklet group	NA	108 (1 study)	⊕⊕⊖⊖ **low**[a,b]	Outcomes pre-specified in the review not reported: reduction of bleedings and emergency department visits, hospital admissions, duration of hospitalisations and the presence of co-morbidities
Cost of psychological intervention Follow-up: NA	Outcome not reported				NA	
Family adjustment Follow-up: NA	Outcome not reported				NA	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **NA**: not applicable; **QoL**: quality of life; **RR**: risk ratio; **VAS**: visual analogue scale

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty: we are very uncertain about the estimate

Footnotes

a. Downgraded once due to risk of bias: study not blinded and incomplete outcome data (45% of randomized participants are not included in analyses)
b. Downgraded once due to applicability: study recruited only adults over the age of 20, therefore results are not applicable to children and adolescents

2 Summary of findings – computerised learning compared to no intervention for hemophilia

Computerised learning compared to no intervention for hemophilia

Patient or population: adults and children with hemophilia

Settings: outpatients

Intervention: computerised learning (e-learning program, computerised educational games, Internet-based self-management and transitional care program) self administered in individual or group situation

Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No intervention	Computerised learning				
Mood or personal well-being: self-efficacy (General Self-Efficacy Scale of Sherer, 5 question scale of Lee) Follow-up: up to 26 weeks	Evidence from 1 trial showed an increase in self-efficacy and 1 trial found no difference in self-efficacy; we are uncertain whether the intervention makes a difference The third trial did not report result for the control group		NA	87 (3 studies)	⊕⊖⊖⊖ **very low**[a,b]	

Coping strategies: disease specific knowledge, practical skills, self management ability and transition readiness Follow-up: up to 26 weeks	1 trial showed an increase from baseline in disease specific knowledge, self management and transition readiness in the Internet program group compared to the no intervention group (within-group difference) 1 trial showed that the e-learning program group improved in practical skills and knowledge from baseline and there was no significant change from baseline in the no intervention group (within-group difference)		NA	47 (2 studies)	⊕⊕⊖⊖ **low**[a]	
QoL: Canadian Haemophilia Outcomes-Kids' Life Assessment Tool (post-treatment scores) Follow-up: up to 26 weeks	The mean QoL score (post-treatment) was 87.6 in the no intervention group	The mean QoL score (post-treatment) was 8.65 lower (18.3 lower to 1.0 higher) in the computerised learning group	NA	17 (1 study)	⊕⊖⊖⊖ **very low**[a,c,d]	
Compliance or adherence to the trial intervention (including satisfaction) Follow-up: up to 26 weeks	The trial reports good participation to the Internet program and general satisfaction for the program		NA	17 (1 study)	⊕⊖⊖⊖ **very low**[a,c]	
Physical health Follow-up: NA	Outcome not reported				NA	
Cost of psychological intervention Follow-up: NA	Outcome not reported				NA	
Family adjustment Follow-up: NA	Outcome not reported				NA	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **NA**: not applicable; **QoL**: quality of life

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty: we are very uncertain about the estimate

Footnotes

a. Downgraded twice due to serious risk of bias: all studies not blinded, some methodological information relating to randomization and allocation concealment unclear, incomplete outcome data in one study (only 44% of randomized participants analysed)
b. Downgraded once due to imprecision: result not reported within control groups
c. Downgraded once due to applicability: adolescents between the ages of 12 and 18 only included in the study, therefore results may not be applicable to other age groups
d. Downgraded once due to imprecision: wide confidence intervals around the effect size

3 Summary of findings - auto-hypnosis (self-hypnosis) compared to control for hemophilia

Auto-hypnosis (self-hypnosis) compared to control for hemophilia

Patient or population: adults and children with hemophilia

Settings: outpatients

Intervention: auto-hypnosis (self-hypnosis).

Comparison: control (usual care or delayed intervention)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Auto-hypnosis (self-hypnosis)				
Mood or personal well-being: change in distress (according to General Severity Index) Follow-up: up to 18 weeks	General Severity Index (GSI) and the subscales measuring anxiety, depression, hostility, phobic anxiety, and obsessive-compulsivity were significantly reduced from baseline. No results were reported for the delayed intervention group		NA	24 (1 trial)	⊕⊖⊖⊖ **very low**[a,b]	
Coping strategies Follow-up: NA	Outcome not reported				NA	
QoL Follow-up: NA	Outcome not reported				NA	
Compliance or adherence to the trial intervention (including satisfaction for it) Follow-up: up to 18 weeks	No correlation was found between hypnotizability of participants (measured by the Harvard Group Scale of Hypnotic Susceptibility) and treatment effect		NA	24 (1 trial)	⊕⊖⊖⊖ **very low**[a,b]	
Physical health: number of bags of blood required, mean factor usage scores Follow-up: up to 40 months	1 study showed there may be a decrease in number of bags of blood needed in the treatment group compared to the control group during the first 10-month treatment period and during the second 10-month treatment period but not during the third 10-month period In the other study, there was a reduction in factor usage in the self-hypnosis group and an increase in factor usage in the control group. This difference was statistically significant ($P < 0.05$)		NA	44 (2 trials)	⊕⊕⊖⊖ **low**[a]	Outcomes pre-specified in the review not reported: hospital admissions, duration of hospitalisations and the presence of co-morbidities or pain intensity.
Cost of psychological intervention Follow-up: NA	Outcome not reported				NA	

Family adjustment Follow-up: NA	Outcome not reported	NA	
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI) **CI**: confidence interval; **NA**: not applicable; **QoL**: quality of life; **RR**: risk ratio			
GRADE Working Group grades of evidence **High certainty**: further research is very unlikely to change our confidence in the estimate of effect **Moderate certainty**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate **Low certainty**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate **Very low certainty**: we are very uncertain about the estimate			

Footnotes

a. Downgraded once due to risk of bias: both studies not blinded, some methodological information relating to randomization and allocation concealment unclear, incomplete outcome data in one study (only 70% of randomized participants analysed)
b. Downgraded twice due to serious imprecision: no specific numerical results reported and results not reported for the control group

4 Summary of findings – relaxation (progressive or self control) compared to no treatment for hemophilia

Relaxation (progressive or self control) compared to no treatment for hemophilia						
Patient or population: adults and children with hemophilia **Settings**: outpatients **Intervention**: relaxation (progressive or self control), delivered by advanced graduate student in clinical psychology **Comparison**: no treatment						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	No treatment	**Relaxation**				
Mood or personal well-being Follow-up: NA	Outcome not reported				NA	
Coping strategies Follow-up: NA	Outcome not reported				NA	
QoL Follow-up: NA	Outcome not reported				NA	
Compliance or adherence to the trial intervention, (including satisfaction) Follow-up: 2 months	Frequency of progressive or self-control relaxation practice was roughly comparable between groups and across phases (mean range, 0.9 to 1.4 per day) The study authors considered the two groups 'highly compliant.'		NA	7 (1 study)	⊕⊖⊖⊖ **very low[a,b]**	

Physical health: Reduction of bleedings, factor replacement, pain Follow-up: 2 months	There may be little or no difference between the two relaxation groups and the control group in the number of bleeds per week The reduction in factor replacement (units) was similar across the two relaxation groups (control group results not reported) There was also no 'discernible' difference in daily tension, arthritic pain and bleeding pain in the two relaxation groups (control group results not reported).	NA	7 (1 study)	⊕⊖⊖⊖ **very low**[a,b,c]	Outcomes pre-specified in the review not reported: hospital admissions, duration of hospitalisations and the presence of co-morbidities or pain intensity
Cost of psychological intervention Follow-up: NA	Outcome not reported			NA	
Family adjustment Follow-up: NA	Outcome not reported			NA	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **NA**: not applicable; **QoL**: quality of life

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty: we are very uncertain about the estimate

Footnotes

a. Downgraded once due to risk of bias: study not blinded and methodological information relating to randomization and allocation concealment unclear
b. Downgraded twice due to serious concerns of applicability: a very small number of participants were randomized and only adults were recruited, therefore results may not be generalisable to a wider population
c. Downgraded once due to imprecision: numerical results not reported for control group

Additional tables

References to studies

Included studies

Beheshtipoor 2015

[CRSSTD: 12959244]

* Beheshtipoor N, Ghanavati SH, Edraki M, Karimi M, Haghpanah S. The effects of computer-based educational games on self-efficacy of 8-12 children with hemophilia. Iranian Journal of Blood and Cancer 2015;7(3):149-54. [CFGD Register: HA141a; CRSREF: 12959245]

IRCT2014101418833N1. Effect of educational video games on self efficacy children. www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT2014101418833N1 2014. [CFGD Register: HA141b; CRSREF: 12959246]

Breakey 2014

[CRSSTD: 12959247]

Breakey VR, Ignas DM, Blanchette VS, Stinson J. The development of an innovative internet-based educational program to promote self-management for teens with hemophilia. Haemophilia 2010;16 Suppl 4:53. [Abstract no.: 12FP01; CFGD Register: HG60a; CRS-ID: 5500125000000075; CRSREF: 12959248]

Breakey VR, Ignas DM, Waria A, White M, Blanchette VS, Stinson J. Feasibility study of a randomized control trial to evaluate an internet-based self-management program for adolescents with hemophilia. Blood 2013;122:2921. [CRSREF: 12959249]

Breakey VR, Ignas DM, Warias A, White M, Blanchette VS, Stinson JN. Feasibility study of a randomized control trial to evaluate an internet-based self-management program for adolescents with hemophilia: preliminary results and observations. Journal of thrombosis and haemostasis : JTH 2013;11 Suppl 2:1058. [Abstract no: PO106; CRSREF: 12959250]

* Breakey VR, Ignas DM, Warias AV, White M, Blanchette VS, Stinson JN. A pilot randomized control trial to evaluate the feasibility of an internet-based self-management and transitional care program for youth with haemophilia. Haemophilia 2014;20(6):784-93. [CFGD Register: HG60d; CRSREF: 12959251]

NCT01477437. Internet-based educational program to promote self-management for teens with hemophilia [Development and evaluation of an internet-based educational program to promote self- management for teens with hemophilia]. clinicaltrials.gov/show/NCT01477437 (first received 22 November 2011). [CRSREF: 12959252]

Elander 2011

[CRSSTD: 12959253]

* Elander J, Robinson G, Morris J. Randomized trial of a DVD intervention to improve readiness to self-manage joint pain. Pain 2011;152(10):2333-41. [CFGD Register: HG61a; CRS-ID: 5500100000011701; CRSREF: 12959254]

Stalker C, Elander J. Effects of a pain self-management intervention combining written and video elements on health-related quality of life among people with different levels of education. Journal of Pain Research 2015;8:581-90. [CENTRAL: 1090094; CFGD Register: HG61b; CRS: 5500050000000420; CRSREF: 12959255; EMBASE: 2015321587]

LaBaw 1975

[CRSSTD: 12959256]

LaBaw WL. Auto-hypnosis in haemophilia. Haematologia 1974;9(1-2):103-10. [CFGD Register: HG14; CRSREF: 12959257]

Lichstein 1985

[CRSSTD: 12959258]

Lichstein KL, Eakin TL. Progressive versus self-control relaxation to reduce spontaneous bleeding in hemophiliacs. Journal of Behavioral Medicine 1985;8(2):149-62. [CFGD Register: HG16; CRSREF: 12959259]

Mulders 2012

[CRSSTD: 12959260]

Breakey VR, Ignas DM, Warias AV, White M, Blanchette VS, Stinson JN. A pilot randomized control trial to evaluate the feasibility of an Internet-based self-management and transitional care program for youth with haemophilia. Haemophilia 2014;20(6):784-93. [CRSREF: 12959261]

E-learning improves knowledge and practical skills in haemophilia patients on home treatment: a randomized controlled trial. Haemophilia 2012;18(5):693-8. Online Data S1: the competence questionnaire to test the knowledge of haemophilia. [CRSREF: 12959262]

Mulders G, De Wee E, Vahedi Nikbakht M, Kruip JH, Elfrink E, Leebeek FW. Haemophilia and home treatment: optimizing knowledge and practical skills by an e-learning program. Journal of Thrombosis and Haemostasis 2013;11 Suppl 2:683. [Abstract no.: PB 2.44-1; CFGD Register: HG62b; CRSREF: 12959263]

* Mulders G, de Wee EM, Vahedi Nikbakht-Van de Sande MC, Kruip MJ, Elfrink EJ, Leebeek FW. E-learning improves knowledge and practical skills in haemophilia patients on home treatment: a randomized controlled trial. Haemophilia 2012;18(5):693-8. [CFGD Register: HG62a; CRS-ID: 5500125000000077; CRSREF: 12959264]

Swirsky-Sacchetti 1986

[CRSSTD: 12959265]

Swirsky-Sacchetti T, Margolis CG. The effects of a comprehensive self-hypnosis training program on the use of factor VIII in severe hemophilia. International Journal of Clinical and Experimental Hypnosis 1986;34(2):71-83. [CFGD Register: HG27; CRSREF: 12959266]

Excluded studies

Beheshtipoor 2012

[CRSSTD: 12959267]

Beheshtipoor N, Bagheri S, Hashemi F, Karimi M. The effect of yoga technique on quality of life in children and adolescents with hemophilia. Haemophilia 2012;18:175. [CRSREF: 12959268]

* Beheshtipoor N, Bagheri S, Hashemi F, Zare N, Karimi M. The effect of yoga on the quality of life in the children

and adolescents with haemophilia. International Journal of Community Based Nursing and Midwifery 2015; 3(2):150-5. [CRSREF: 12959269]

Cuesta-Barriuso 2014

[CRSSTD: 12959270]

Cuesta-Barriuso R, Torres-Ortuño A, López-García M, Nieto-Munuera J. Effectiveness of an educational intervention of physiotherapy in parents of children with haemophilia. Haemophilia 2014;20(6):866-72. [CRSREF: 12959271]

Cuesta-Barriuso 2018

[CRSSTD: 12959272]

Cuesta-Barriuso R, Gomez-Conesa A, Lopez-Pina JA. Manual and educational therapy in the treatment of hemophilic arthropathy of the elbow: a randomized pilot study. Orphanet Journal of Rare Diseases 2018; 13(1):151. [CFGD Register: HG106b; CRSREF: 12959273]

Cuesta-Barriuso R, Torres-Ortuno A, Nieto-Munuera J, Lopez-Pina JA. Safety and efficacy of manual and educational therapy in the treatment of hemophilic arthropathy of the elbow. A randomized clinical trial. Haemophilia 2018;24(Suppl 1):42. [CFGD Register: HG106a; CRSREF: 12959274]

NCT02198040. Physiotherapy in the haemophilic arthropathy of the elbow. https://clinicaltrials.gov/show/NCT02198040 (date first posted 23 July 2014). [CFGD Register: HG106c; CRSREF: 12959275]

Dunne 1991

[CRSSTD: 12959276]

Dunne PW, Sanders MR, Rowell JA, McWhirter WR. An evaluation of cognitive-behavioural techniques in the management of chronic arthritic pain in men with haemophilia. Behaviour Change 1991;8(2):70-8. [CRSREF: 12959277]

Firoozabadi 2012

[CRSSTD: 12959278]

Firoozabadi M D, Mahdavinejad R, Ghias M, Rouzbehani R, Dehghani M. The effects of an exercise therapy program on joint range of motion, aerobic fitness, and anxiety of hemophilia A patients. Journal of Isfahan Medical School 2012;30(177):106-14. [CFGD Register: HA128; CRSREF: 12959279]

Heydari 2018

[CRSSTD: 12959280]

Heydari MG, Shirazi M, Sanagouyemoharer GR. The effect of positive psychotherapy in test anxiety among zahedan students with hemophilia. Research in psychotherapy: psychopathology, process and outcome 2018; 21(1):55-61. [CFGD Register: HG108; CRSREF: 12959281]

ISRCTN63283043

[CRSSTD: 12959282]

ISRCTN63283043. Nurse-facilitated adherence therapy for haemophilia. www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN63283043 2014. [CFGD Register: HG111; CRSREF: 12959283]

Kang 2012

[CRSSTD: 12959284]

Kang HS, Kim WO, Jeong Y, Kim SY, Yoo KY. Effect of a self-help program for mothers of hemophilic children in Korea. Haemophilia 2012;18(6):892-7. [CRSREF: 12959285]

Magli-Barioz 2004

[CRSSTD: 12959286]

Magli-Barioz D, Ounnoughène N, Paugy P, Quarrè MC, Vassilief D, Lopez, I, et al. Evaluation of the impact of information about treatment-related risks in patients receiving blood-derived or recombinant medications. Haemophilia 2004;10(5):572-81. [CRSREF: 12959287]

NCT02198014

Unpublished data only [CRSSTD: 12959288; ClinicalTrials.gov: Manual Therapy in Haemophilic Arthropathy of the Knee (ARTHROPA). NCT02198014]

NCT02198014. Manual Therapy in Haemophilic Arthropathy of the Knee (ARTHROPA). https://clinicaltrials.gov/ct2/show/NCT02198014 (first posted 23 July 2014). [CRSREF: 12959289]

NCT02825706

[CRSSTD: 12959290]

[CRSSTD: 12959290]

NCT02825706. Educational physiotherapy in haemophilia. https://clinicaltrials.gov/show/NCT02825706 2016. [CFGD Register: HG113; CRSREF: 12959291]

NCT03136003

Unpublished data only [CRSSTD: 12959292; ClinicalTrials.gov: DDAVP vs. Exercise in Patients With Mild Hemophilia A NCT03136003]

NCT03136003. DDAVP vs. Exercise in Patients With Mild Hemophilia A. https://clinicaltrials.gov/ct2/show/NCT03136003 (first posted 2 May 2017). [CRSREF: 12959293]

Omura 2013

[CRSSTD: 12959294]

Omura K, Ito M, Eguchi E, Imahuku K, Kutsumi M, Inoue Y, et al. The effect of peer support groups on self-care for haemophilic patients with HIV in Japan. Haemophilia 2013;19(6):876-81. [CRSREF: 12959295]

Parsons 2000

[CRSSTD: 12959296]

Parsons JT, Huszti HC, Crudder SO, Rich L, Mendoza J. Maintenance of safer sexual behaviours: evaluation of a theory-based intervention for HIV seropositive men with haemophilia and their female partners. Haemophilia 2000;6(3):181-90. [CRSREF: 12959297]

Penica 2008

[CRSSTD: 12959298]

Penica S, Williams KE. The use of a psychological intervention to increase adherence during factor administration in a child with haemophilia. Haemophilia 2008;14(5):939-44. [CRSREF: 12959299]

Sergis-Deavenport 1983

[CRSSTD: 12959300]

Sergis-Deavenport E, Varni JW. Behavioral assessment and management of adherence to factor replacement therapy in hemophilia. Journal of Pediatric Psychology 1983;8(4):367-77. [CRSREF: 12959301]

Slifer 2009

[CRSSTD: 12959302]

Slifer KJ, DeMore M, Vona-Messersmith N, Pulbrook-Vetter V, Beck M, Dalhquist L, et al. Comparison of two brief parent-training interventions for child distress during parent-administered needle procedures. Children's Health Care 2009;38(1):23-48. [CRSREF: 12959303]

Thomas 2001

[CRSSTD: 12959304]

Thomas D, Gaslin TC. "Camping up" self-esteem in children with hemophilia. Issues in Comprehensive Pediatric Nursing 2000;24(4):253-63. [CRSREF: 12959305]

Von Mackensen 2012

[CRSSTD: 12959306]

Von Mackensen S, Eifrig B, Zäch D, Kalnins J, Wieloch A, Zeller W. The impact of a specific acqua-training program for adult haemophilic patients-results of the WATERCISE study. Haemophilia 2012;18:714-21. [CRSREF: 12959307]

Walker 2004

[CRSSTD: 12959308]

Walker I, Sigouin C, Sek J, Almonte T, Carruthers J, Chan A, et al. Comparing hand-held computers and paper diaries for haemophilia home therapy: a randomized trial. Haemophilia 2004;10(6):698-704. [CRSREF: 12959309]

Wincott 1976

[CRSSTD: 12959310]

Wincott EAIMSW. Psychosocial aspects of hemophilia: problems, prevention, treatment modalities, research, and future directions. Mount Sinai Journal of Medicine 1976;44(3):438-55. [CRSREF: 12959311]

Studies awaiting classification

Kang 2005

[CRSSTD: 12959312]

Kang HS, Kim WO, Lee HS. Effects of a self-help group program for young adults with hemophilia. Taehan Kanho

Hakhoe Chi 2005;35(3):602-10. [CRSREF: 12959313]

Karimi 2014

[CRSSTD: 12959314]

Karimi S, Hoorfar H, Setaki Y. The effect's of logotherapy on self-concept scale in Iranian patients with severe hemophilia A: Seyed Alshohada hospital in Isfahan province. In: Haemophilia. Vol. 20 Suppl 2. 2014:24. [CRSREF: 12959315]

Ongoing studies

IRCT201502079267N4

[CRSSTD: 12959316]

IRCT201502079267N4. The effect of psychological empowerment on psychological outcome in hemophiliac adolescents [The effect of psychological empowerment on using coping mechanisms, stress, anxiety and depression in hemophiliac adolescents in comparison without taking it]. www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT201502079267N4 (date of registration 25 July 2015). [CFGD Register: HG110; CRSREF: 12959317]

IRCT20180311039037N1

[CRSSTD: 12959318]

IRCT20180311039037N1. Effect of Benson relaxation on hemophilia disease [Effect of Benson relaxation on intensity, acceptance and belief of pain in hemophilia patients]. www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20180311039037N1 (date of first registration 07 October 2018). [CFGD Register: HG115; CRSREF: 12959319]

NCT03529474

Unpublished data only [CRSSTD: 12959320; ClinicalTrials.gov: Psychology and Physiotherapy Approach of Chronic Pain in Patients With Hemophilia. NCT03529474]

NCT03529474. Psychology and physiotherapy approach of chronic pain in patients with hemophilia [Nonpharmacological Approach of Chronic Pain in Patients With Hemophilia: a Combined Approach From Psychology and Physiotherapy]. https://clinicaltrials.gov/ct2/show/NCT03529474 (first posted 18 May 2018). [CRSREF: 12959321]

Pinto 2016

Published and unpublished data [CRSSTD: 12959322; ClinicalTrials.gov: Effectiveness of Psychological Interventions in Haemophilia (PSY_HaEMOPEQ). NCT02870452]

NCT02870452. Effectiveness of psychological interventions in haemophilia. https://clinicaltrials.gov/show/NCT02870452 (first posted 17 August 2016). [CRSREF: 12959323]

Pinto PR, Paredes AC, Costa P, Carvalho M, Lopes M, Fernandes S, et al. Effectiveness of two psychological interventions for pain management, emotional regulation and promotion of quality of life among adult Portuguese men with haemophilia (PSY-HaEMOPEQ): study protocol for a single-centre prospective randomised controlled trial. BMJ Open 2017;7(9):e016973. [CRSREF: 12959324]

Other references

Additional references

Albrecht 1999

Albrecht G, Devlieger P. The disability paradox: high quality of life against all odds. Social Science and Medicine 1999;48(8):977-88.

Barlow 2007

Barlow JH, Stapley J, Ellard DR, Gilchrist M. Information and self-management needs of people living with bleeding disorders: a survey. Haemophilia 2007;13(3):264-70.

Beeton 2005

Beeton K, Neal D, Lee C. An exploration of health-related quality of life in adults with haemophilia--a qualitative perspective. Haemophilia 2005;11(2):123-32.

Beeton 2007

Beeton K, Neal D, Watson T, Lee CA. Parents of children with haemophilia – a transforming experience. Hhaemophilia 2007;13:570-579. [DOI: 10.1111/j.1365-2516.2007.01494.x]

Bosscher 1998

Bosscher RJ, Smit JH. Confirmatory factor analysis of the General Self-Efficacy Scale. Behaviour Research and Therapy 1998;36(3):339-43.

Bottos 2007

Bottos AM, Zanon E, Sartori MT, Girolami A. Psychological aspects and coping styles of parents with haemophilic child undergoing a programme of counselling and psychological support. Haemophilia 2007;13(3):305-10.

Bradley 2008

Bradley PM, Landsay B.. Care delivery and self-management strategies for adults with epilepsy. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD006244 DOI: 10.1002/14651858.CD006244.pub2.

Budzynski 1973

Budzynski TH, Stoyva JM, Adler CS, Mullaney DJ. EMG biofeedback and tension headache: a controlled outcome study. Psychosomatic Medicine 1973;35(6):484-96.

Cassis 2007

Cassis FR. Psychosocial care for people with hemophilia. World Federation of Hemophilia. Treatment of Hemophilia series 2007;No 44.

Deakin 2005

Deakin TA, McShane CE, Cade JE, Williams R.. Groupbased training for self-management strategies in people with type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD003417 DOI: 10.1002/14651858.CD003417.pub2.

Deeks 2011

Deeks JJ, Higgins JP, Altman DG on behalf of the Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analysis. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Derogatis 1977

Derogatis LR. SCL-90-R. Administration, Scoring and Procedures Manual-I for the Revised Version. Baltimore, MD: Johns Hopkins University School of Medicine Press, 1977.

Dunn 2008

Dunn N, Miller R, Griffioen A. How does being a carrier affect women and their partners: experience in the UK. Haemophilia 2008;14(Suppl 2):129. [Abstract no.: #29 FP09]

Effing 2007

Effing T, Monninkhof EM, van der Palen J, van Herwaarden CLA, Partidge MR, Walters EH, et al.. Self-management education for patients with chronic obstructive disease. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD002990 DOI: 10.1002/14651858.CD002990.pub2.

Elander 2008

Elander J, Robinson R. A brief haemophilia pain coping questionnaire (HPCQ). Haemophilia 2008;14(5):1039-48.

Elander 2009

Elander J, Robinson G, Mitchell K, Morris J. An assessment of the relative influence of pain coping, negative thoughts about pain, and pain acceptance on health-related quality of life among people with hemophilia. Pain 2009;145(1-2):169-75.

Emiliani 2010

Emiliani F, Palareti L, Melotti G. Families with chronically ill children: Studies and research perspectives [Famiglie con bambini affetti da malattia cronica: Prospettive di studio e di ricerca]. Psicologia Clinica dello Sviluppo 2010; 14(2):233-266. [DOI: 10.1449/32687]

Emiliani 2011

Emiliani F, Bertocchi S, Potì S, Palareti L. Process of normalization in families with children affected by hemophilia. Qualitative Health Research 2011;21(12):1667-1678. [DOI: 10.1177/1049732311417456]

Ghanizadeh 2009

Ghanizadeh A, Baligh-Jahroni P. Depression, anxiety and suicidal behaviour in children and adolescents with hemophilia. Haemophilia 2009;15(2):528-32.

Gibson 2002

Gibson PG, Powell H, Wilson A, Abramson MJ, Haywood P, Bauman A, et al.. Self-management education and regular practitioner review for adults with asthma. Cochrane Database of Systematic Reviews 2002, Issue 3. Art. No.: CD001117 DOI: 10.1002/14651858.CD001117.

Hays 1993

Hays RD, Sherbourne D, Mazel RC. The RAND 36-item health Survey 1.0. Health Economics 1993;2(3):217-27.

Hays 2001

Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Annals of Medicine 2001; 33(5):350-7.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327(7414):557-60.

Higgins 2011

Higgins JP, Deeks JJ, Altman DG on behalf of the CSMG. Chapter 16: Special topics in statistics. In: Higgins JP, Green S, editor(s). Cochrane Handbook of Systematic Reviews of Interventions. Version 5.1 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hoots 2007

Hoots WK, Shapiro AD. Genetics of the hemophilias. www.uptodate.com/contents/genetics-of-the-hemophilias?source=search_result&search=haemophilia&selectedTitle=3%7E114 (accessed 01 December 2011).

Iorio 2010

Iorio A, Matino D, D'Amico R, Makris M. Recombinant Factor VIIa concentrate versus plasma derived concentrates for the treatment of acute bleeding episodes in people with haemophilia and inhibitors. Cochrane Database of Systematic Reviews 2010, Issue 8. Art. No.: CD004449 DOI: 10.1002/14651858.CD004449.pub3.

Iorio 2011

Iorio A, Marchesini E, Marcucci M, Stobart K, Chan AK. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD003429 DOI: 10.1002/14651858.CD003429.pub4.

Jensen 2003

Jensen MP, Nielson WR, Kerns RD. Towards the development of a motivational model of pain self-management. Journal of Pain 2003;4(9):477-92.

Kerns 1997

Kerns RD, Rosenberg R, Jamison RN, Caudill MA, Haythornwaite J. Readiness to adopt a self-management approach to chronic pain: the Pain Stages of Change Questionnaire (PSOCQ). Pain 1997;72(1):227-34.

Kessler 2006

Kessler CM, Mariani G. Clinical manifestations and therapy of the hemophilias. In: Colman RW, Clowes AW, Goldhaber SZ, Marder VJ, George JN, editors(s). Hemostasis and Thrombosis: Basic Principles and Clinical practice. Lippincott Williams & Wilkins, 2006:887-904.

Khair 2010

Khair K. Minimizing joint damage: the role of nurses in promoting adherence to hemophilia treatment.. Orthopaedic Nursing 2010;29(3):193-200.

Kirkham 2017

Kirkham JJ, Davis K, Altman DG, Blazeby JM, Clarke M, Tunis S, et al. Core Outcome Set-STAndards for Development: the COS-STAD recommendations. PLOS Medicine 2017;14:e1002447. [DOI: 10.1371/journal.pmed.1002447]

Lee 1994

Lee C, Bobko P. Self-efficacy beliefs: comparison of five measures. Journal of Applied Psychology 1994;79:364-9.

Lozier 2004

Lozier JN, Kessler CM. Clinical aspects and therapy of hemophilia. In: Hoffman R, Benz-Jr EJ, Shattil SJ, Furie B, Cohen HJHJ, Silberstein LE, editors(s). Hematology Basic Principles and Practice. 4th edition. Elsevier, 2004:2047-69.

McCracken 2004

McCracken LM, Vowles KE, Eccleston C. Acceptance of chronic pain: component analysis and a revised assessment method. Pain 2004;107(1):159-66.

MECIR 2012

Higgins JP, Lasserson T, Chandler J, Tovey D, Churchill R. Methodological Expectations of Cochrane Intervention Reviews (MECIR) version 1.07 (updated November 2018). The Cochrane Collaboration, 2018. Available from https://community.cochrane.org/mecir-manual.

Mulder 2004

Mulder K, Cassis F, Seuser DR, Narayana SR, Dalzell R, Poulsen W. Risks and benefits of sports and fitness activities for people with haemophilia. Haemophilia 2004;10 Suppl 4:161-3.

Nation 2003

Nation M, Crusto C, Wandersman A, Kumpfer KL, Seybolt D, Morrissey-Kane E, et al. What works in prevention: principles of effective prevention programs. American Psychologist 2003;58(6-7):449.

Plug 2008

Plug I, Peters M, Mauser-Bunschoten EP. Social participation of patients with hemophilia in the Netherlands. Blood 2008;111(4):1811-5.

Remor 2002

Remor E, Arranz P, Miller R. Psychosocial impact of inhibitors on haemophilia patients' quality of life. In: Rodrigues-Merchan EC, Lee C, editors(s). Inhibitors in patients with haemophilia. Oxford: Blackwell Science, 2002:187-92.

RevMan 2014

Review Manager 5 (RevMan 5) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rodgers 1999

Rodgers GM, Greenberg CS. Inherited Coagulation Disorders. In: Lee GR, Foerster J, Lukens J, Paraskevas F, Greer JP, Rodgers GM, editors(s). Wintrobe's Clinical Hematology. 10th edition. Baltimore: Lippincott Williams & Wilkins, 1999:1682-732.

Roosendaal 2006

Rosendaal G, Lafeber FP. Pathogenesis of haemophilic arthropathy. Haemophilia 2006;12 Suppl 3:117-21.

Sansom-Daly 2012

Sansom-Daly UM, Peate M, Wakefield CE, Bryant RA, Cohn RJ.. A systematic review of psychological interventions for adolescents and young adults living with chronic illness.. Health Psychology 2012;31(3):380-93.

Savage 2014

Savage E, Beirne PV, Ni Chroinin M, Duff A, Fitzgerald T, Farrell D. Self-management education for cystic fibrosis. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD007641 DOI: 10.1002/14651858.CD007641.pub3.

Shaw 2007

Shaw EJ, Strokes T, Camosso-Stefinovic J, Baker R, Baker GA, Jacoby A. Self-management education for adults with epilepsy. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD004723 DOI: 10.1002/14651858.CD004723.pub3.

Sherer 1982

Sherer M, Maddux JE, Mercandante B, Prentice-Dunn S, Jacobs B, Rodgers R. The self-efficacy scale: construction and validation. Psychological Reports 1982;51(2):663-71.

Shor 1962

Shor RE, Orne EC. Harvard Group Scale of Hypnotic Susceptibility, Form A. Palo Alto, CA: Consulting Psychologists Press, 1962.

Siboni 2009

Siboni SM, Mannucci PM, Gringeri A, Franchini M, Tagliaferri A, Ferretti M, et al. Health status and quality of life of elderly persons with severe hemophilia born before the advent of modern replacement therapy. Journal of Thrombosis and Haemostasis 2009;7(5):780-6.

Small 2009

Small SA, Cooney SM, O'Connor C. Evidence-informed program improvement: using principles of effectiveness to enhance the quality and impact of family-based prevention programs. Family Relations 2009;58(1):1-13.

Stieltjes 2009

Stieltjes N, Torchet MF, Misrahi L, Roussel-Robert V, Lambert T, Guérois C, et al. Epidemiological survey of haemophiliacs with inhibitors in France: orthopaedic status, quality of life and cost--the 'Statut Orthopedique des Patients Hemophiles' avec Inhibiteur study. Blood Coagulation and Fibrinolysis 2009;20(1):4-11.

Stokes 2007

Stokes T, Shaw EJ, Camosso-Stefinovic J, Baker R, Baker GA, Jacoby A.. Self-management education for children

with epilepsy. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD004724 DOI: 10.1002/14651858.CD004724.pub3.

Talaulikar 2006

Talaulikar D, Shadbolt B, McDonald A, Pidcock M. Health-related quality of life in chronic coagulation disorders. Haemophilia 2006;12(6):633-42.

Villaça 2004

Villaça PR, Carneiro JD, D'Amico EA. Hemofilias. In: Zago MA, Falcão RP, Pasquini R, editors(s). Hematologia Fundamentos e Prática. São Paulo: Editora Atheneu, 2004:803-18.

von Mackensen 2004

Von Mackensen S, Bullinger M. Development and testing of an instrument to assess the quality of life of children with haemophilia in Europe (Haemo-QoL). Haemophilia 2004;10 Suppl 1:17-25.

von Mackensen 2007

Von Mackensen S. Quality of life and sports activities in patients with haemophilia. Haemophilia 2007;13 Suppl 2:38-43.

Williams 2011

Williams TS, Sherman EM, Dunseith C, Mah JK, Blackman M, Latter J, et al. Measurement of medical self-management and transition readiness among Canadian adolescents with special health care needs. International Journal of Child and Adolescent Health 2011;3(4):527-35.

Yorke 2005

Yorke J, Fleming SL, Shuldham C.. Psychologicalinterventions for children with asthma. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD003272 DOI: 10.1002/14651858.CD003272.pub2.

Yorke 2006

Yorke J, Fleming SL, Shuldham C.. Psychological interventions for adults with asthma. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD002982 DOI: 10.1002/14651858.CD002982.pub3.

Young 2006

Young NL, Bradley CS, Wakefield CD, Barnard D, Blanchette VS, McCusker PJ. How well does the Canadian Haemophilia Outcomes-Kid's Life Assessment Tool (CHO-KLAT) measure the quality of life of boys with haemophilia? Pediatric Blood & Cancer 2006;47(3):305-11.

Other published versions of this review

Cassis 2012

Cassis F, Emiliani F, Pasi J, Palareti L, Iorio A. Psychological interventions for people with hemophilia. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD010215 DOI: 10.1002/14651858.CD010215.

Classification pending references

Data and analyses

1 DVD plus information booklet compared to information booklet alone

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Coping strategies - Pain Stages of Change Questionnaire	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.1.1 Pre-contemplation (at 6 months)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.1.2 Contemplation (at 6 months)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.1.3 Action / maintenance (at 6 months)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.2 Coping strategies - Haemophilia Pain Coping Questionnaire	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.2.1 Active coping (at 6 months)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.2.2 Negative thoughts (at 6 months)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.2.3 Passive adherence (at 6 months)	1		Mean Difference(IV, Fixed, 95% CI)	No totals

1.3 Coping strategies - Chronic Pain Acceptance Questionnaires	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.3.1 Activity engagement (at 6 months)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.3.2 Pain willingness (at 6 months)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.4 Health-related QoL - RAND 36	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.4.1 Physical domain (at 6 months)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.4.2 Mental domain (at 6 months)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.5 Adherence: use of intervention at least once	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
1.6 Physical health: pain intensity (VAS, 6-month post treatment scores)	1		Mean Difference(IV, Fixed, 95% CI)	No totals

2 Computerised learning compared to no intervention

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Mood and personal well-being: self-efficacy according to GSE-S 12 scale (change from baseline)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
2.2 Coping strategies: disease-specific knowledge	1		Mean Difference(IV, Fixed, 95% CI)	No totals
2.3 Coping strategies: self-management ability and transition readiness (change from baseline)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
2.4 Health-related QoL - CHOK-LAT (post-program score)	1		Mean Difference(IV, Fixed, 95% CI)	No totals

3 Auto-hypnosis (self-hypnosis) compared to usual care

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Physical health - change from baseline in number of bags of blood used (90 AHF units)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
3.1.1 During the first 10 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
3.1.2 During the second 10 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
3.1.3 During the third 10 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
3.1.4 Across the total 30 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals

4 Progressive relaxation compared to no treatment

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Physical health - reduction in the number of bleeds per week	1		Mean Difference(IV, Fixed, 95% CI)	No totals

5 Self-control relaxation compared to no treatment

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Physical health - reduction in the number of bleeds per week	1		Mean Difference(IV, Fixed, 95% CI)	No totals

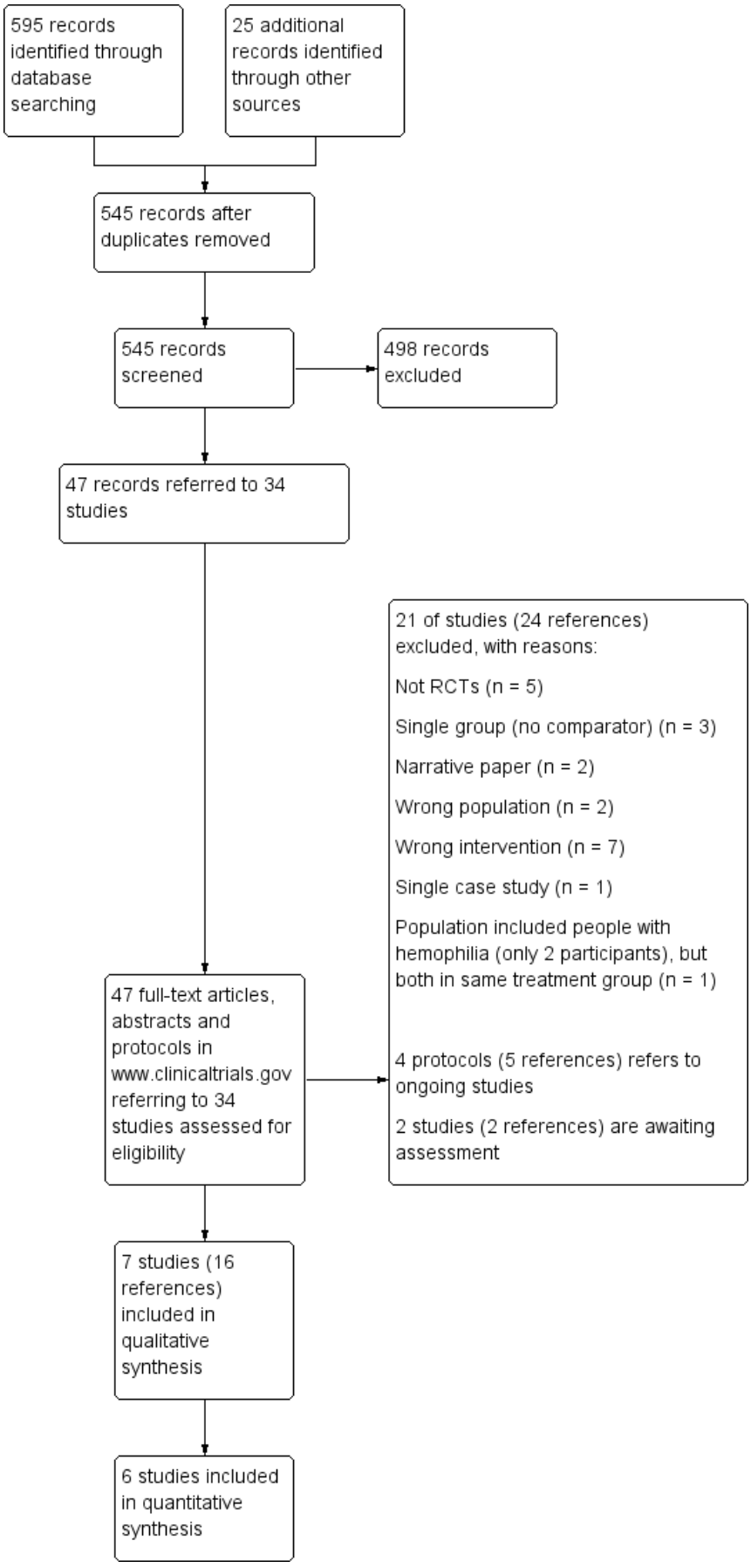
6 Progressive relaxation compared to self-control relaxation

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

6.1 Physical health - reduction in the number of bleeds per week	1		Mean Difference(IV, Fixed, 95% CI)	No totals

Figures

Figure 1



Caption

Caption

Study flow diagram

Sources of support

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK
  This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

Feedback

Appendices

1 Glossary

Term	Definition
By-pass agents	Clotting factor concentrates (factor VIII inhibitor bypass activity or FEIBA and activated recombinant factor VII (rFVIIa) available for the treatment of bleeds in patients with inhibitors.
Carrier	A female who has a gene for hemophilia. It is used to refer to a female who carries the gene but has not the symptoms.
Comprehensive care	Medical care that covers several aspects of patient´s well-being and health - mental, emotional, physical. A comprehensive care team is multidisciplinary including hematologists, nurses, social workers, psychologists, physiotherapists, dentists, orthopedic surgeon and genetic counsellors.
Concentrate	A sterile freeze-dried, powdered product containing coagulation factors such as factor VIII or factor IX for example. Such products may be produced from recombinant technology or derived from large pools of human plasma. Plasma donations used for such products are screened for contaminating viruses such as HIV, Hepatitis B and C before use and then either heat treated, pasteurized or solvent -detergent treated to further eliminate any residual virus and protect against viral transmission.
Cryoprecipitate	The material precipitated from fresh frozen plasma when it is thawed slowly at 2 to 4°C. Cryoprecipitates are rich in coagulation factors VIII, XIII, VWF, fibronectin and fibrinogen. This solid remaining protein is re-dissolved by warming to give a small volume of cryoprecipitate solution which can be used to treat hemophilia A.
Epistaxis	Bleeding from the nostril or nasopharynx.
Factor	Blood components that help clot blood. Factor VIII and Factor IX are two of these components.
Factor VIII and Factor IX concentrates	See 'Concentrate' above.
Fresh frozen plasma (FFP)	Plasma separated from whole blood by centrifugation, which is then frozen to below -30°C within 8 hours of collection. This plasma contains all coagulation proteins and clotting factors and is used widely as a replacement therapy for coagulation problems. Historically it was the only source of factor VIII and IX and the only treatment available for treatment of hemophilia. In the developed world it has been superseded by factor concentrates as a source of factor VIII and IX. It remains an important treatment for hemophilia in less well developed areas where concentrates and cryoprecipitate may not be freely and easily available. Most FFP is not virus inactivated.
Hemarthrosis	Bleeding or hemorrhage into joints.
Hematuria	Presence of blood in the urine.
Hematoma	A localized swelling filled with blood (bruise) resulting from bleeding.
Iliopsoas bleeding	The large group of muscles in the hip area. Bleeding in these muscles is a significant problem as large quantities of blood can accumulate in these muscle and nerve compression may occur as a direct result.

Term	Definition
Immune tolerance induction treatment (ITI)	A treatment to attempt to eradicate inhibitors in patients by continued exposure to factor VIII or IX. Such regimens comprise may be either low dose or high dose concentrate regimes. It is a complex treatment with many issues to consider, e.g. costs, variation in responses and complications dependent on subtype hemophilia (A or B), use of plasma derived or recombinant concentrates, use of adjuvant immunosuppressants.
Inhibitor	Antibodies to factor VIII or factor IX that inhibit the biological function of the coagulation factor. Patients with hemophilia develop inhibitors as alloantibodies, that is an antibody to a protein that is recognized as foreign. It is considered the most serious complication in hemophilia.
On demand therapy	One of the models of treatment for people with hemophilia where clotting factor concentrate are infused when bleeding occurs.
Port-A-Cath	Also called implantable venous access device (VAD) is a medical device that is implanted under the skin, usually on the chest wall. It is a titanium reservoir unit connected to a catheter tube which is tunnelled under the skin and surgically inserted into a vein. The reservoir unit, which has a robust silicone self sealing bubble to allow insertion of a needle, is easily felt and provides a large target area that more easily allows to injection and infusion of intravenous medications. It is frequently used in children or other patients where access to veins to give intravenous injections is problematic. In patients with hemophilia is often used to simplify regular prophylaxis and immune tolerance treatments.
Prophylaxis	The regular infusion of factor concentrates to prevent bleeding in patients with hemophilia. Infusions are given every twice or three times a week or on alternate days dependent on type of hemophilia and patient requirements. Prophylaxis is either primary or secondary. Primary prophylaxis is the use of prophylaxis to prevent bleeding or joint damage that is commenced before any joint bleeding or damage has occurred. It is therefore usually started before 2 years of age. Secondary prophylaxis is prophylaxis commenced after joint bleeding or joint damage has occurred to prevent further deterioration or progression.
Recombinant factor VIII and IX	Factor VIII and IXconcentrates produced using recombinant DNA technology. Being free of human proteins such products are not at risk of transmission of blood borne viruses and deemed very safe. Later generation products are also produced in an environment free of adjuvant animal proteins.
Symptomatic carrier	A female that, when having the gene for hemophilia, has also reduced factor activity level (generally less than 50%) that places the individual at risk of bleeding.

2 Search strategies

Database	Search terms	Date searched
CINAHL	1 TX experimental OR TX randomized OR TX RCT OR TX trial 2 TX haemophilia OR hemophilia 3 TX therapy OR TX intervention* OR TX program* OR TX support 4 TX psy* OR TX socio* OR TX educat* 5 AND 1-4	07 June 2018
MEDLINE	1 (experimental or randomized or RCT or trial).af. 2 (haemophilia or hemophilia).af. 3 (intervention* or therapy or program* or support).af. 4 (psy* or socio* or social* or educat*).af. 5 AND 1-4	07 June 2018
PsycINFO	1 h?emophilia.mp. or exp Hemophilia/ 2 (experimental or trial or RCT or randomized).af. 3 (intervention or therapy or program or support).af. 4 (psy* or socio* or social* or educat* or manag*).af. 5 AND 1-4	07 June 2018
Embase	1 (hemophilia or haemophilia).af. 2 (experimental or trial or RCT or randomized).af. 3 (intervention or therapy or program).af. 4 (psy* or socio* or social* or educat*).af. 5 AND 1-4	30 March 2018
ClinicalTrials.gov	1 interventional studies 2 1 AND (haemophilia or hemophilia). AND psychological 3 1 AND (haemophilia or hemophilia). AND education 4 1 AND (haemophilia or hemophilia). AND social	30 March 2018
WHO ICTRP	1 CONDITION: haemophilia OR haemophilia ['Without Synonyms' box selected] 2 INTERVENTION: psychology OR psychological OR cognitive OR psychodynamic OR psychosocial OR social OR psychotherapy OR counselling OR counseling OR behavioural OR behavioral OR behaviour OR behavior OR education OR educational OR family OR families OR cope OR coping 3 RECRUITMENT STATUS: All	06 September 2019