Observational Prolonged Trial in Myotonic Dystrophy type 1 to Improve Qol Standards, a Taget Identification Collaboration.

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Primary ObjectiveTo evaluate the effect of a tailored behavioral change intervention comprising CBT and physical activity on participation (as measured by the DM1-Activ scale) for severely fatigued patients with myotonic dystrophy type 1 compared to...

Ethical review	Approved WMO
Status	Pending
Health condition type	Neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON38289

Source
ToetsingOnline

Brief title
OPTIMISTIC

Condition

- Neuromuscular disorders

Synonym
Myotonic Dystrofy type 1 and Dystrofia Myotonica (DM1)

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: Europese Unie

Intervention

Keyword: Cognitive Behavioural Therapy, Dystrofia Myotonica, Exercise therapy, Intervention

Outcome measures

Primary outcome

2.2 OUTCOMES

See Appendix 1 for the trial outcome measurement schedule.

2.2.1 Primary Outcome

The primary outcome measure will be the DM1-Activ measured at the end of the 10-month intervention period. DM1-Activ is a specific outcome measure of activity and participation for patients with DM1 [Hermans 2010].

Secondary outcome

2.2.2 Secondary Outcomes

Activity (50 mins)

• 6-minute walk test (6MWT) with BORG Scale assessment (0-10 Rating of Perceived Exertion score)

• (Activities of Daily Living (ADL) assessment)

• Myotonic Dystrophy Health Index (MDHI)

• Physical activity measured with actometer (NB: participants take this home after each visit and wear for 2 weeks).

Fatigue and sleepiness (10 mins)

• Fatigue and Daytime Sleepiness Scale (FDSS)

• Checklist Individual Strength (CIS) fatigue

Quality of life (20 mins)

• Individualised Neuromuscular Quality of Life Questionnaire (InQoL)

Mood (15 mins)

• Beck Depression Inventory for Primary Care

Cognitive (20 mins)

• Apathy evaluation scale (AES)

• Stroop test

2.2.3 Measures used as potential effect modifiers

We will collect some data to evaluate their potential as modifiers of the

effect seen in the trial:

• Muscular impairment rating scale (MIRS)

• McGill pain questionnaire

• CBT questionnaires (self-efficacy scale for fatigue (SES-28); Fatigue

catastrophising scale (FCS); Focusing on symptoms (IMmQ); Illness acceptance

scale; Social support (SSL-D).

• Trail making

• Adult Social Behavior Questionnaire (ASBQ)

2.2.4 Identification of Biomarkers and expansion of CTG repeats

Whole blood will be collected in a standardised manner from all 286 DM1 participants enrolled in the trial, with 3x 10ml whole blood samples and up to 20ml urine sample collected per patient. These will be used for biomarker identification and for genetic work linked to CTG repeats.

Identification of biomarkers

mRNA and microRNA expression changes in serum samples will be collected for each participant in the trial (ie. 286 DM1 patients). In particular, attention will be paid to the expression of candidate microRNAs relevant to the following targets in addition to any others selected from initial next generation RNA sequencing studies in the discovery cohorts:

• insulin receptor

• muscle chloride channel

• SERCA1

• RyR1 and

• troponin T

The following microRNA targets will be assessed in addition to any further selections based on other sources:

• miR-1

• miR-133b

• miR-29 and

• miR-206

Expansion of CTG repeats

The blood samples collected for DNA extraction will also be collected at the baseline and at the end of the observation period (ie. 16 months after the start of the intervention or control). Also historical DNA samples will be collected if available to inform analysis of disease progression. DM1 is caused by the expansion of CTG repeats in the DMPK gene. Disease severity is correlated with the number of repeats. However, the CTG repeats are highly unstable and the number of repeats changes from one generation to the next and throughout life. Recent data have indicated that the major modifier of disease severity is the number of CTG repeats inherited and that disease severity is further modified by the individual specific rate of somatic expansion (Morales et al., 2012; Higham et al., 2012). The time series of DNA samples collected will be used to estimate the number of repeats inherited and monitor the rate of change of the repeat length over time in each patient

Study description

Background summary

DM1 is a rare, inherited, progressive disease as well as an autosomal dominant multisystemic disorder. It is the most common adult form of muscular dystrophy, with a prevalence of approximately 10 per 100,000 people affected (Norwood 2009, Norman 1989). With 733 million people in Europe, we estimate that 75,000 people are DM1 patients in Europe (European Commission 2011). Typical symptoms of the disease include progressive muscle weakness and wasting from distal to

proximal, ptosis, weakness of facial, jaw and anterior neck muscles, myotonia, daytime sleepiness, fatigue and cataract. Other symptoms of adult DM1 include cardiac conduction defects, as well as endocrine, gastrointestinal and cognitive dysfunction. DM1 is one of the most variable human diseases, has complex, multisystemic and progressively worsening clinical manifestations and leads to severe physical impairment, restricted social participation and premature death (Gagnon 2008; Kierkegaard 2011).

There is no pharmaceutical treatment for causal or symptomatic relief of DM1 core symptoms (with the exception of Modafinil for excessive daytime sleepiness). Thus the aim of treatment is to relieve impairments, reduce limitations and optimise participation. Physical activity has been acknowledged as an important factor for health in general. For patients with a slowly progressive neuromuscular disease, such as DM1, there is accumulating evidence for prescribing low-to-moderate-intensity strength and aerobic exercise training, and an active lifestyle (Cup 2007, Pedersen 2006). Nevertheless, recent reviews conclude that existing studies are limited in number and quality, and that there is a need for disease-specific, randomised, controlled trials investigating the effect on quality of life (Cup 2007, Voet 2010, Voet 2013).

Study objective

Primary Objective

To evaluate the effect of a tailored behavioral change intervention comprising CBT and physical activity on participation (as measured by the DM1-Activ scale) for severely fatigued patients with myotonic dystrophy type 1 compared to standard care.

2.1.2 Secondary Objectives
• Creation and introduction of evidence based clinical guidelines on exercise and cognitive behavioural therapy in DM1.
• Identification of individual (serum, DNA) or composite biomarker profiles as surrogate outcome measures and moderating or mediating factors of the efficacy and safety of the clinical response.
• Create clinical trial infrastructure for European DM1 trials, including the collection of natural history data from a large cohort of DM1 patients.

Study design

2.1 STUDY DESCRIPTION
OPTIMISTIC is a two-arm, multi-centre, randomised controlled trial designed to compare a tailored behavioural change intervention against standard patient management regimes. It is expected that the trial and outcome work will lead to new clinical guidelines for DM1 management. The intervention comprises

cognitive behavioural therapy (CBT) and graded physical activity, both of which aim to achieve a more active lifestyle.

The effectiveness of this intervention, together with any adverse events associated with it, will be compared to standard patient management. Outcome measures will be measured at baseline, 5 months, 10 months (the end of the intervention period) and at 6-months post intervention (ie. 16 months from baseline, Figure 2).

See OPTIMISTIC Patient Pathway (Figure 2.) on page 11 of the studyprotocol
See 2.2 Study flowchart (figure 3) on page 12 of the studyprotocol
See 2.3 TRIAL OUTCOME MEASUREMENT SCHEDULE appendix 1

Intervention

5.1 Behavioral change intervention

In the OPTIMISTIC STUDY patients in the treatment arm will receive cognitive behaviour therapy (CBT). CBT is aimed at reducing the level of disabilities of patients by addressing three core problems thought to maintain disabilities: 1) severe fatigue; 2) a reduced initiative and 3) suboptimal interaction with significant others. It is assumed that CBT will reduce these problems and thus enable DM1 patients to become more active. The intervention is based on a model of fatigue and disability in DM1 and evidence-based cognitive behavioural interventions for patients with other chronic medical conditions. Intervention group participants will receive continue to receive standard clinical care as judged necessary by their treating clinicians.

Note: some parts of the intervention are targeted at the caregiver or significant other. If a DM1 patient has no caregiver or significant other, or no caregiver or significant other willing to take part in the study, the patient will NOT be excluded from the study. For brevity, we will use *caregiver* in the following text but this should be taken as meaning *caregiver or significant other*.

CBT consists of six different modules. All patients will start with individual goal setting and psycho-education about the role of cognitive-behavioural variables in the disabilities patients* experience. The patient formulates his or her treatment goals in concrete terms and later on in the therapy the goals are realised step by step by the patient. The treatment is tailored to the patient*s problems: which of the six modules a patient will receive is dependent on the scores on measures that have been collected at baseline assessment. The extra measures for the baseline assessment will take about 40 minutes. They will be used to assess elements relevant for CBT that will direct the intervention. The extra measures will also enable us to do mediation analysis to determine to what extent the changes in cognitions and behaviour mediate the expected positive effects of the intervention on the outcome

measures. If a patient is not able to fill in the questionnaires, it is unlikely that the patient can profit from the intervention and will not be randomised. Based on our previous experience with modular interventions we expect that most patients will receive less than four modules. The six modules are:

1. Learning to compensate for a reduced initiative. After psycho-education patients learn how to compensate for a reduced initiative by using cues to initiate activity. Examples of these cues are using a diary, mobile phone with an alarm or the scheduling of activities. Caregivers will also be taught how to cue behaviour and how to stimulate the patients to use cues. The goal of this module is to help the patient to start more activities. This module is indicated if a patient scores higher than 38 on Apathy Evaluation Scale (AES). The AES is filled in by the caregiver and/or CBT therapist during the intake session. The caregiver is asked to participate in the intervention and to fill in some of the questionnaires. However, if the caregiver refuses or cannot participate, the patient can still take part in the trial.
2. Suboptimal interaction with caregivers. The disabilities associated with DM1 put considerable strain on caregivers and can also lead to a negative interaction with the patient. The patient can also feel misunderstood by others, which further hampers the interaction with others. The goal of this module is to optimise the interaction with caregivers by installing realistic expectations about what can be expected from the patient, teach caregivers how to help patients to stay as self-reliant as possible and also reduce caregivers strain by taking time for themselves. The expectations of the patient about the support of others will be discussed and the patient is stimulated to adequately ask for support where possible. This module is indicate if 1) a proxy scores 7 or higher on the Caregiver Strain Index (CSI) or 2) the partner and/or patient score 60 or lower on the Marital Satisfaction VAS or 3) the patient score 14 or higher on the subscale discrepancy (SSI-D) of the social support inventory (short form).

The following 4 modules are specifically aimed at fatigue maintaining behaviours and beliefs:

3. Regulation of the sleep-wake pattern. The importance of a regular sleep-wake cycle and a good sleep hygiene are discussed, and instructions will be given how to improve both. At baseline patients will register bedtime, get-up times and sleeping during the day for 2 weeks. This will be noted by the patients using a diary. This is plotted in a bar chart to visualize irregularities in the patient*s sleep-wake cycle. This module is indicated if the patient has an irregular sleep-wake cycle and/or scores 60 or higher on the subscale sleep of the Sickness Impact Profile (SIP).
4. Reformulation of dysfunctional cognitions with respect to fatigue and/or DM1. At baseline the sense of control over fatigue symptoms, fatigue catastrophising and the tendency to focus on fatigue are assessed. This module is indicated if a patient has a problematic score on one or both of the

following instruments: Self-efficacy Scale for fatigue (score 19 or lower), and the Fatigue Catastrophising Scale (score 16 or higher) or a score of 4 or higher on the Illness Management questionnaire. Helping beliefs with respect to fatigue are formulated and patient practise with them. Patients will also practice with redirecting the focus of attention away from the fatigue toward activity and other sensations. If a patient has dysfunctional beliefs about the illness, example given has difficulty accepting the fact of being ill, helping belief will be formulated. This intervention will be done if a patient scores in the problematic range on the Pictorial Representation of Self and Illness Measure (PRISM), the Beck Depression Inventory (BDI-PC >=4) or subscale Illness acceptance (<=12).
5. Activity regulation and graded activity. Physical activity will be assessed using an ankle or wrist worn actometer (GeneActiv / Kinesense or equivalent CE marked device). The device is light weight, waterproof and has been adapted for long wear. It is ofen worn by sports men and woman to measure activity progress. Full detailed instructions will be given to the patients at the baseline visit. The device will be attached using a non-metal bracelet and patients will be instructed that it should be worn for 14-days continuously but that it can be easily removed by the participant if required by cutting the bracelet with a pair of scissors. The actometer will we worn for 14-days after the baseline assessment to define what activity measures are in place. Relatively active patients first have to distribute their activities more evenly followed by a gradual increase of physical activity. At baseline patients will choose an activity programme with the counsellor, either a low intensity, graded physical activity program and an exercise program aimed at an increased physical fitness:
a. a program aimed at gradually increasing the time that they walk, OR
b. an exercise program aimed at increasing their physical fitness. The exercise programme will be defined through the counselling but will target incorporating moderate intensity exercises such as walking, cycling, jogging or dancing for at least half an hour, three times a week. After participants have increased their physical activity level or fitness they start to increase other activities in order to reach their goals.
The Actometer
The device will be worn for 14-days continuously after baseline and at months 5, 10 and 16. Additional use may also be suggested by the counselling to assist behaviour change. The device will be fitted at a visit, worn for 14-days, removed and then returned to the trial site by post in stamped addressed padded envelope. The actometer itself is a tri-axial STMicroelectronics accelerometer and the acceleration will be sampled at 50 Hz. Raw data is transferred through USB to PC and analyses according to patient ID on MOVEeCloud.

Non-Wear time
Results for a given 14-day period will be deemed invalid if non-wear time exceeds 50% duration. Where non-wear time is less than 50% the results will still be used and the non-wear time will be accounted for by imputation of the

non-wear time using available wear time data at similar times on other days for the given participant.

Control
Those not randomised to the intervention will also be invited to wear the actometer for 14-days immediately after visits at baseline, months 5, 10 and 16. The device will be returned by post in the same was as for intervention group participants.

6. Coping with pain with a focus on dysfunctional cognitions with respect to pain. Dysfunctional pain cognitions are disputed. More helpful pain related cognitions will be installed. This module is indicated if a patient has a problematic score on the SF36 pain subscale (score lower than 60) or 44 on the VAS pain.

The intervention will be delivered by therapists who have received extensive training and will use a standardised treatment manual developed by the OPTIMISTIC team. Prior to participating in the graded activity module, the treating clinician will make a judgment as to the degree of physical activity the participant is safely capable of doing, which will be communicated to the therapists. The therapists will remain in contact with the treating clinician throughout the trial to discuss any changes. The Therapists and/or the Research Nurse can request that the treating physician/Investigator to review the patient at any time if any of the research team, the patient or the carer have any concerns. . If required the patients* GP will be informed.

Participants will receive a workbook containing relevant information and assignments. If deemed appropriate a patient may be given a gym membership to assist with their set goals. If participants give their permission, sessions will be audio recorded and transcribed. Transcriptions will be anonymised. Audio recordings will be stored securely at local sites and destroyed as per 11.2 Study record retention.

Between sessions participants will do *home-work* assignments that are discussed in the subsequent session. If caregivers are involved in the intervention, they will be asked to support the patient in carrying out these assignments. Treatment integrity will be determined by two experienced cognitive behavioural therapists, who will independently rate a random selection of the sessions. During the intervention period phone calls to participants will be made at least once a week between sessions to remind them to complete any homework and to ensure attendance at sessions. Where it is felt necessary and resources allow participants will be visited in their homes to increase adherence and provide support where needed.

The intervention runs for ten months but is front-loaded, meaning the first four months can be considered the *active* phase with the remaining six months in the *booster* phase. In this period of ten months a patient will receive

10-14 sessions, at least five of them are face to face session. For the other sessions the therapist can decide, dependent on the traveling distance and the mobility of the patient, to use telephone contact or video conferencing as an alternative.

In addition, all therapists will receive one support call every two weeks by telephone from an experienced cognitive behavioural therapist in the OPTIMISTIC team, with extra support available by email.

5.2 Comparison
Standard care is the usual care at the participating site. This will vary by site and according to individual patient symptoms but the minimum is generally an annual visit plus ECG. Other care may include appropriate history taking, physical examination, ECG/EKG (or more in depth cardiac investigations), pulmonary and gastrointestinal investigations, and rehabilitation measures.

All control group participants will visit their trial site at baseline, months 5, 10 and 16 post intervention (ie. 16 months from baseline) for the measurements as detailed in Appendix 1.

Study burden and risks

The patients need extra visits to the outpatient clinic or other research areas of the hospital. In addition, the venapunction causes sometimes discomfort for an individual patient. The participants have to answer many questions about symptoms of the myotonic dystrophy disease. The patient should wear an actometer ("watch-like") attached to the ankle, four times over a period of 14 consecutive days, that detects exercise. Wearing the actometer can cause some discomfort in the daily life. And divided into the interventiuon groep the level of fatigue may increase temporarily, because of the more exercise.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients DM1, genetically proven
Older than 18 years
CIS fatigue score >35

Exclusion criteria

Severe depression at screening
Neurologische of orthopedische co-morbiditeit
Unable to complete study questionnaires

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2014
Enrollment:	72
Type:	Anticipated

Ethics review

Approved WMO Date:	18-03-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-05-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-10-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-02-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	04-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Not approved	
Date:	09-12-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	
Date:	07-03-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	
Date:	23-06-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL46914.091.13