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Botulinum toxin as a new treatment modality for jerky psychogenic movement disorders: a randomized controlled trial

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PROTOCOL TITLE

Botulinum toxin as a new treatment modality for jerky psychogenic movement disorders: a randomized controlled trial

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**
BoNT	**Botulinum neurotoxin**
CGI	**Clinical Global Impression scale**
EMG	**Electromyogram**

EEG	**Electroencephalogram**
NSAID	**Non steroidal anti-inflammatory drug**
UMRS	**Unified Myoclonus Rating Scale**
ALDS	**AMC Linear Disability Scale**
SF-36	**Short form-36**
MINI	**Mini International Neuropsychiatric Interview**
PUTS	**Premonitory Urge for Tics Scale**
CRU	**Clinical Research Unit**
MRC	**Medical Research Counsil**

SUMMARY

Rationale: Botulinum neurotoxin (BoNT) has emerged as a useful therapy for several movement disorders associated with muscle overactivity such as dystonia and jerky movement disorders. At least 2–9% of patients seen in movement disorder clinics suffer from movement disorders with a psychogenic origin and a substantial part of them has jerks. These psychogenic jerky movement disorders cannot be accounted for by a known neurologic syndrome. Therapy of psychogenic jerks currently focuses on frequently co-occurring psychiatric disease, but results are poor. In this project, we will study the effect of BoNT on movement disorders of psychogenic origin.

Objective: To evaluate the effect of treatment with BoNT on psychogenic jerks.

Study design: A monocenter study consisting of two parts: a double-blind randomized placebo controlled intervention study of 16 weeks and an uncontrolled follow-up study of one year to evaluate the long-term effects of BoNT.

Study population: Patients with at least one invalidating consistent type of psychogenic jerk that is present for 1 year or longer.

Intervention: During the trial phase of the study, patients will receive two BoNT or placebo injections with an interval of 3 months. The number of muscles injected and the doses to be administrated in an individual patient will be determined by an experienced neurophysiologist analogous to treatment of dystonia. Hereafter, for the follow-up study all patients will receive 4 BoNT injections at intervals of 3 months. **Main study parameters/endpoints:**

Primary outcome measure: To assess whether treatment with BoNT leads to improvement of psychogenic jerks according to an independent movement disorder specialist assessed with the Clinical Global Impression - Improvement scale.

Secondary outcome measures are the effect of BoNT on: the severity of jerks according to a movement disorder specialist; improvement and severity of the jerk according to the patient; nature and severity of overall dyskinesia; jerk frequency; whether patients consider treatment with BoNT effective; disability; quality of life; co-existent psychiatric disorders and the occurrence of adverse reactions; muscle weakness. Additionally in approximately 16 patients a resting state fMRI will be performed before and after the treatment intervention (16 weeks after start of the treatment). Analysis of the comparison before and after treatment will be done by a researcher blinded for the intervention.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

The risks associated with participation in this study are low: BoNT is considered a safe therapy in other movement disorders. The most common side effects of BoNT are local weakness and pain and side effects are reversible. The neuropsychological and psychiatric questionnaires used in our study are considered to be mildly psychologically stressful.

Functional magnetic resonance imaging is a non-invasive and safe procedure and is very commonly used in clinical practice and research.

1. INTRODUCTION AND RATIONALE

Botulinum neurotoxin (BoNT) has emerged as a useful therapy for several movement disorders associated with muscle overactivity. When BoNT is injected in the muscles, the toxin produces local chemodenervation by blocking the release of acetelylcholine at the neuromuscular junctions. It thereby renders the muscle (partially) unable to contract for a period of 3 to 4 months. The most common side effects of BoNT are local weakness and pain. These side effects are reversible as well.[1]

BoNT is an effective treatment for several disorders, for example for cervical dystonia and blepharospasm, diseases for which therapeutic options previously were restricted.[2]

Botulinum toxin seems a promising therapy for other movement disorders associated with muscle overactivity as well, including jerky movement disorders.[2] We hypothesize that BoNT is an effective treatment for jerky movement disorders of psychogenic origin.

Psychogenic movement disorders are disorders that cannot be accounted for by any known neurologic ("organic") syndrome and encompass a diversity of hyperkinetic movements.[3] Psychogenic movement disorders are amongst the commonest of unexplained neurological symptoms and are supposed to exist in at least 2–9% of patients seen in movement disorder clinics.[4] Of patients with psychogenic movement disorders, 22% were shown to have psychogenic jerks (myoclonus and tics).[5] Although there are some general features common to all functional movement disorders, diagnosis may be difficult. Diagnosis of functional jerks however is largely assisted by the results of EMG and EEG. When the EEG consistently shows a characteristic pre-movement potential (Bereitschaftspotential), the diagnosis psychogenic jerks can be made quite certain.[5]

When patients with psychogenic neurological symptoms are compared to those with symptoms associated with organic disease, they are found to have similar disability and more distress.[6] Psychogenic movement disorders often coexist with psychiatric disease: 38% of patients were shown to have an axis I diagnosis (mostly depression and anxiety disorders) and 42% had an axis II diagnosis (personality disorder).[3] In general, patients with psychogenic movement disorders are treated multidisciplinary by a psychiatrist, neurologist and often a physical therapist. The effects of treatment are unsatisfactory: after an interval of 3.2 – 6 years, 65 – 90% of the treated patients still has a psychogenic movement disorder.[5] An important factor associated with poor outcome is long duration of symptoms.[3]

It is gradually becoming clear that the distinction between organic and psychogenic disorders is not as black-and-white as was previously thought.[7, 8] Psychogenic and organic dystonia for example share similar neurophysiologic abnormalities. Besides, it appears that abnormal sensory input from repetitive movements can produce changes in the central nervous system. It has been hypothesized that these central changes can participate in maintaining

the movement disorder (i.e. dystonia). In such a situation, treatment of the psychiatric disturbances alone may not be enough to alleviate the disorder.[9] Treatment with BoNT might restore the changes in the central nervous system via normalisation of movement patterns. Although no studies have been published on the effect of treatment with BoNT on psychogenic movement disorders, our own clinical experience clearly suggests improvement.

Recently our research group was the first to perform an fMRI study concerning patients with psychogenic jerks in an attempt to gain more insight in the pathophysiology of this disorder (MEC# 07/290). However no imaging studies have ever been performed to evaluate treatment effect in psychogenic movement disorders. Therefore we would like to perform a functional magnetic resonance imaging study in a small sample of our patient population to evaluate the BoNT treatment and to improve knowledge on pathophysiology and diagnostics of psychogenic jerks.

2. OBJECTIVES

Objectives of the randomized placebo controlled trial:

Primary Objective:

To assess whether treatment with BoNT improves motor characteristics of an invalidating jerk of interest in patients with psychogenic jerks according to a movement disorder specialist.

Secondary Objectives:

To asses, in patients with psychogenic jerks, the effect of treatment with BoNT on:

- the severity of the invalidating jerk of interest scored by a movement disorder specialist;
- improvement of motor characteristics and severity of the invalidating jerk of interest scored by the patient;
- the nature, distribution and severity of overall dyskinesia, scored by a movement disorder specialist;
- the frequency of the invalidating jerk of interest;
- whether patients consider treatment with BoNT effective and whether they judge that the benefits of treatment outweigh the side-effects;
- disability;
- quality of life;
- co-existent psychiatric disorders;
- the occurrence of adverse reactions;
- muscle weakness;
- difference in brain function measured by fMRI

Objectives of the follow-up study:

To asses, in patients with psychogenic jerks, the long-term effect of treatment with BoNT on:

- improvement of motor characteristics and severity of the invalidating jerk of interest scored by a movement disorder specialist ;
- improvement of motor characteristics and severity of the invalidating jerk of interest scored by the patient;
- the nature, distribution and severity of overall dyskinesia, scored by a movement disorder specialist;
- the frequency of the invalidating jerk of interest;

- whether patients consider treatment with BoNT effective, whether they judge that the benefits of treatment outweigh the side-effects and what they think about which treatment they have received (placebo or BoNT);
- disability;
- quality of life;
- co-existent psychiatric disorders;
- the occurrence of adverse reactions;
- muscle weakness.

3. STUDY DESIGN

This project consists of two parts: a randomized placebo-controlled trial to assess the short-term effect of treatment of BoNT on psychogenic jerks and an uncontrolled follow-up study to assess the long-term effect.

Study population

A total of 54 patients with one or more jerks of psychogenic origin will be included in the study. To be included, patients need to experience to be significantly impaired in daily functioning due to at least one specific jerk. For the trial phase of the study, patients will be randomized in a 1:1 ratio to treatment with BoNT or to treatment with placebo. After 16 weeks, when the trial phase of the study is over, all patients will be included in the study on the long-term effect of treatment. Patients with serious complications during the trial period will not be included in second part of the study. For our fMRI sub-study approximately 16 patients of our total study population will be included. They will be compared to 16 neurologically and psychiatrically healthy volunteers.

Intervention

BoNT or placebo (0.9% sterile saline) will be injected in muscles involved in the jerky movement. In appearance the placebo is indistinguishable from BoNT. The muscles that will be injected will be determined by a neurophysiologist experienced in treatment with BoNT according to the pattern of movements visible and according to the involved muscles measured with EMG. The number of muscles injected may differ per patient. The neurophysiologist will determine the doses to be administered. These will be similar to those used for involvement of the same muscle by other movement disorders (typically dystonia). Placebo injections consist of an equivalent volume of 0.9% sterile saline. All injections will be given by an experienced neurophysiologist, who will remain blind to the treatment allocation and will not be involved in the outcome assessments.

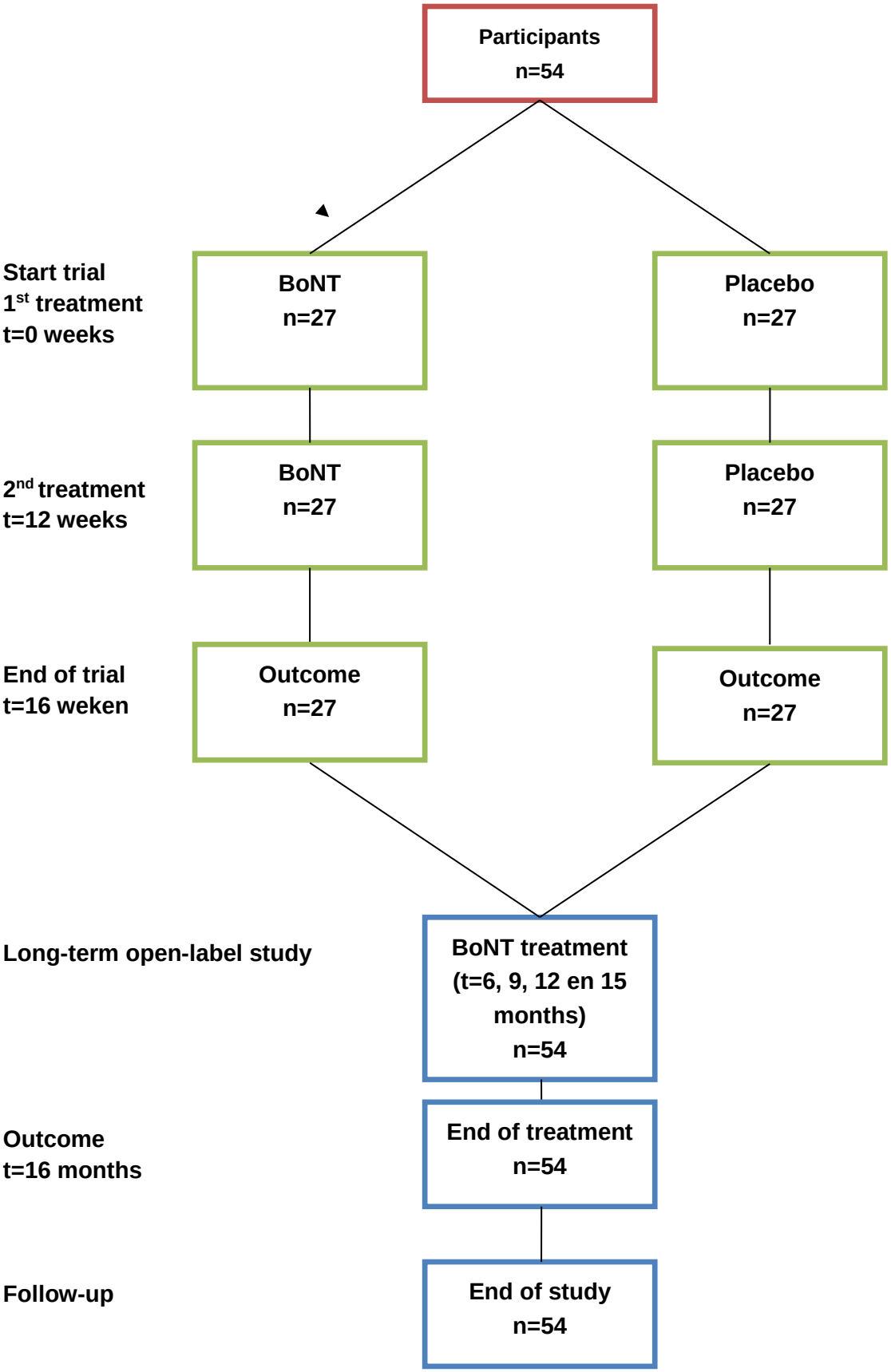
As dose response differs individually, patients will be treated two times. The first treatment will take place after the baseline assessment. The second treatment will take place 3 months hereafter; this is the usual time interval in the treatment of dystonia. To optimize therapy, the dose and if necessary the injection sites may be adjusted in the second session according to degree of response and occurrence of muscle weakness. After 16 weeks, the trial period ends (see also time scheme, page 14).

After the trial period, all patients will be assigned to treatment with BoNT to establish the long-term effects. In this phase of the study, patients will receive a total of 4 times injections with BoNT at 3 month intervals. This results in a follow-up period of 12 months for all patients included in the study. The length of this follow up is considered necessary because of

several reasons. First and most important, an effect of therapy may diminish over time in these patients with a chronic disorder with frequently co-occurring disease. Second, it is considered an evaluation period for certain secondary study objectives, as it may take longer than the trial period before an effect on for example, concurrent psychiatric disease is observed. Finally, this way it is possible to evaluate whether optimalization of treatment results in better response to therapy in these patients.
Additionally in 16 of 54 patients an fMRI scan will be performed before and at the end of the trial (16 weeks).

Assessments

Patients will be assessed at baseline, 16 weeks (the trial period) and after 16 months (follow-up study). Information on improvement, severity and frequency of jerks, the effect of therapy, disability and psychiatric disorders will be acquired with an interview and with questionnaires. Furthermore patients will be neurologically examined and recorded on video. A small part of the patients (n=16) will undergo an fMRI scan before and after treatment.


Participants
n=54
Start trial
1st treatment
t=0 weeks
BoNT
n=27
Placebo
n=27
2nd treatment
t=12 weeks
BoNT
n=27
Placebo
n=27
End of trial
t=16 weken
Outcome
n=27
Outcome
n=27
Long-term open-label study
BoNT treatment
(t=6, 9, 12 en 15
months)
n=54
Outcome
t=16 months
End of treatment
n=54
Follow-up
End of study
n=54

4. STUDY POPULATION

4.1 Population

Patients with one or more jerks of psychogenic origin that significantly disable them in their daily functioning will be included in the study. Patients will be recruited in several manners. The patients with psychogenic jerks enrolled in an ongoing study focussing on the pathophysiology of jerky movement disorders will be evaluated for eligibility, (METC number 07/290) suitable patients from our outpatient clinic will be asked to participate and movement disorder specialists from other clinics will be asked to refer suitable patients.
Approximately 16 of the 54 patients participating in the BonT study will be included to take part in the fMRI study. These patients will be included at the UMC Groningen and will be included, irrespective of the randomised group that they're in. Furthermore 16 healthy control subjects will be included. Controls need to be healthy, both neurological and psychiatric, and are age- and gender- matched with the participants with psychogenic movement disorder. Controls on medication that affect the brain (like benzodiazepines/opiates/barbiturates) or with a history of substance abuse are excluded from this study.

4.2 Inclusion criteria

Eligible patients for the study have at least one consistent type of jerk of psychogenic origin. Two movement disorder specialists have to agree on the diagnosis based on clinical characteristics and on additional investigations if considered necessary. The diagnosis of psychogenic jerks needs to have a "definite" or "probable" level of certainty for psychogenic movement disorders.[10] To be included, patients need to experience to be significantly impaired in daily functioning due to one specific jerk. The jerk of interest needs to be performed by a muscle or muscles amendable to injection and may be simple or complex if only treatment with BoNT is considered possible. No change in medication in the month prior to participation is allowed.

4.3 Exclusion criteria

- Age < 18 years or > 80 years;
- Psychogenic jerk of interest present for < 1 year;
- Previous or current treatment with BoNT;
- Pregnancy;
- Coagulation disorders;
- Insufficient knowledge of Dutch language.
- Legally incompetent adult

- No informed consent
- Patients carrying medical/metal devices or with extreme claustrophobia (only when participating in the fMRI study)

4.4 Sample size calculation

No prior results are available to clearly base the sample size calculation on. Hence, we chose to base our calculation on an expected difference in proportions reaching the primary endpoint between treatment with BoNT and placebo. For the expected proportions, we took the results of two prior trials studying the effect of BoNT into account. First, a trial in writer's cramp showed an effect in 32% of patients allocated to placebo and in 70% of patients allocated to BoNT on a patient rated primary endpoint.[11] Second, a cross-over trial in patients with motor tics showed no change in tics per minute in patients treated with placebo. Patients with tics and dystonia often have concurrent psychiatric disease as well. [12, 13] As the placebo effect may be large in patients with psychogenic disorders,[14] we expect that approximately one third of patients allocated to placebo treatment and approximately two thirds of patients allocated to BoNT may reach the primary endpoint. A two group Chi-square test with a 0,05 two-sided significance level will have 80% power to detect the difference between a control group proportion of 0,30 and a treatment group proportion of 0,70 (odds ratio of 5,4) when the sample size in each group is 24. As the side effects of therapy are mild and self-limiting and because only two injections are given in the trial period, we expect practically no withdrawals in this phase of the study. Assuming a withdrawal rate of 10 percent, we plan to include 27 patients per treatment arm, which means 54 patients in total.

This sample size calculation only concerns the trial part of this study, no power analysis was done for the follow-up study.

Regarding the fMRI study approximately 16 of the 54 patients participating in the BonT study will be included to take part in the fMRI study. Based on a study by Thirion et al., a minimum of 16 subjects is required for fMRI studies (see also amendment 2).

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Patients will be randomized to treatment with:

- 2 times injections with botulinum neurotoxin injections intramuscular with a 3 month interval

or

- 2 times injections of placebo intramuscular with a 3 month interval.

Placebo will consist of 0.9% sterile saline. This is a frequently used placebo in studies on botulinum toxin. [11, 15]

After the trial period, all patients will receive 4 injections of BoNT also with 3 month intervals.

5.2 Use of co-intervention

During the study, the patients continue their previously prescribed therapy. Patients will not be allowed to use medication (benzodiazepines, opiates, barbiturates) in such dosages that it might affect the performance on neuropsychological tests. No change in medication in the month prior to participation is allowed. During the study, changes in concurrent medication will be discouraged but will be registered if they do occur.

5.3 Escape medication

If patients experience adverse effects like pain or flu like symptoms, usage of NSAID or paracetamol is allowed, no interactions with BoNT have been described.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Name and description of investigational medicinal product(s)

Dysport®, botulinum neurotoxin type A, will be compared to placebo (sterile saline).

6.2 Summary of findings from non-clinical studies

There is no pre-clinical information that has not been included in sections of the Summary of Product Characteristics of Dysport® (pg.7- 9).

6.3 Summary of findings from clinical studies

In the clinical trial programme, approximately 28% of the patients treated with Dysport® experienced an adverse event. The following adverse reactions were seen in patients treated across a variety of indications including blepharospasm, hemifacial spasm, torticollis and spasticity associated with either cerebral palsy or stroke:

- Rare: neuralgic amyotrophy
- Uncommon: itching
- Rare: skin rashes

Common side effects are: generalised weakness, fatigue, flu-like syndrome, pain / bruising at injection site.

No side effects have been found in clinical studies concerning placebo (see SPC sterile saline).

6.4 Summary of known and potential risks and benefits

Dysport® is contraindicated in individuals with known hypersensitivity to any components of Dysport®, careful consideration should be given before the injection of patients who have experienced a previous allergic reaction to a product containing botulinum toxin type A Side effects related to spread of toxin distant from the site of administration have been reported, which in some cases was associated with dysphagia, pneumonia and /or significant debility.. The occurrence of these side effects though are rare. Common side effects are: generalised weakness, fatigue, flu-like syndrome, pain / bruising at injection site. These side-effects are reversible and may be expected to resolve within two to four weeks.
No potential risk factors have been described concerning placebo(see SPC placebo).

6.5 Description and justification of route of administration and dosage

Dysport® is only available as powder for injection, after dissolving it is a colourless fluid indistinguishable from sterile saline. Both Dysport® and sterile saline will be administrated by intramuscular injection. The muscles that will be injected will be determined by a neurophysiologist experienced in treatment with BoNT according to the pattern of movements visible and according to the involved muscles measured with EMG. If more jerks are eligible, one jerk of interest will be selected by the patient prior to the first administration. During the entire study, therapy will be aimed at this particular jerk. The number of muscles injected may differ per patient.

6.6 Dosages, dosage modifications and method of administration

For individual patients, the dose of botulinum toxin to be injected will be determined based on the number and type of muscles that are involved in performing the jerk. The muscles that will be injected will be determined by a neurophysiologist experienced in treatment with BoNT according to the pattern of movements visible and according to the involved muscles measured with EMG. Hereafter the local farmacy will prepare the determined dosage of BoNT or sterile saline 0.9%. In this manner the neurophysiologist will remain blinded. The dosage of BoNT depends on the volume of the muscle(s) it is injected in and guidelines for starting dosages and for adjustments after the first injection for individual muscles exist. These guidelines will be used for the treatment of psychogenic jerks in this study.[16] Because the dosage of BoNT depends on the muscles to be injected, individual patients will receive different dosages. The dilution volume of Dysport will be 500 units in 2.5 cc of 0.9% saline. If there is no effect of the treatment the the first time, the dosage will be doubled during second treatment. The maximum dosage per treatment session is 400 Dysport units. BoNT is an accepted and widely-used therapy for dystonia and as such a great deal of experience is available.

6.7 Preparation and labelling of Investigational Medicinal Product

Dysport® and placebo will be prepared, blinded and labelled by Ipsen BV, a pharmaceutical company that works according to GMP guidelines. The medication will be transported to the pharmacy of the Academic Medical Center, where it will be checked and approved. To remain double blind the local pharmacy of the Academic Medical Center will prepare botulinum toxin or placebo, according to the dosage determined by the neurophysiologist, for the individual patients according to a randomization list. This is necessary because BoNT is may only be stored for up to 8 hours following reconstitution. The syringes will not contain

information on the allocated treatment. This way the person that performs the injection, the patients and other persons involved in the trial, will remain blind for the supplied therapy.

6.8 Drug accountability

Dysport and placebo will be requested from its direct supplier, Ipsen BV. To remain double blind the local pharmacy of the Academic Medical Center will prepare placebo or botulinum toxin for the individual patients according to a randomization list. The syringes will not contain information on the allocated treatment.

If any study medication remains at the end of the study, the medication will be returned to the AMC pharmacy, where it will be destroyed.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The primary study endpoint for the trial will be improvement of motor characteristics of the jerk of interest assessed with the Clinical Global Impression - Improvement scale (CGI-I). On this 7 point scale can be assessed how much the patients illness has improved or worsened relative to the baseline state. It can be rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.[17] We will consider a score 1, 2 or 3 determined by an experienced researcher as reaching the primary outcome. The primary outcome will be determined 4 weeks after the second injection (t=16 weeks) as the optimal effect of BoNT is between 4 and 8 weeks after the injection. One researcher who is blind to allocated treatment will assess the CGI-I in all patients based on videos of the patient.
The CGI-I scale is one of the few rating scales that is considered suitable for psychogenic movement disorders at this moment.[18]

7.1.2 Secondary study parameters/endpoints

1. Clinical Global Impressions-Severity of Illness Scale (CGI-S) for motor severity of illness, including other jerks, rated by the investigator;[17]
2. Severity and improvement of the jerk of interest according to the patient. The CGI-I will be used for the improvement of the jerk of interest, including other jerks, rated by the patient;[17] The severity will be measured using the CGI-S and the Visual Analogue Scale(VAS). This is a self assessment scale drawn by the patient on a 10 cm line, on which 0 indicates no disease burden and 10 indicates the worst possible disease burden; [11]
3. Severity of general dyskinesia and myoclonus according to a movement disorder specialist using two scales; the unified myoclonus rating scale (UMRS) [19], which measures the nature, distribution and severity of dyskinesia and a recently developed PMD scale, which quantifies the impact of the movements and is a valid measure of severity. It is used to assess PMDs and test the efficacy of intervention strategies;[18]
4. Frequency of the jerk of interest during the psychiatric interview;
5. The patients answer to the following questions: considering all advantages and disadvantages of this treatment, is the improvement such that you want to continue this treatment or not? [11]

6. AMC Linear Disability Score (ALDS), a generic instrument which includes ADL and instrumental activities of daily living;[20, 21]
7. Short-Form-36(SF-36), a generic Quality of Life scale, suitable for measuring disease burden and health benefits produced by a wide range of different treatments;[22]
8. Psychiatric evaluations including the Mini-International-Neuropsychiatric Interview – Plus (MINI-Plus) and several questionnaires concerning symptoms of depression, anxiety and obsessive-compulsive disorders. The Yale Tic severity scale[23] and the Premonitory Urge for Tics Scale (PUTS)[24], will be used for assessment of tics and evaluation of premonitory urge in the jerk of interest;
9. Evaluation of adverse effects via interview and neurological examination;
10. MRC scale for testing muscle strength and sensibility;
11. Changes in brain function assessed with fMRI.

Outcome measures 2, 5, 6, and 7 will be completed by the patients. Measure 1, 3 and 4 will be based on the video recordings and will be completed by the same independent investigator who is blind to treatment and is not involved in the injections based on the video of the patients. The psychiatric evaluations will be performed by a neuropsychologist specifically trained to perform the MINI-plus psychiatric interview.
A time schedule of the study is presented at page 14. For the trials secondary outcome measures, similar to the primary outcome measure, the difference in scores between baseline and after 16 weeks (4 weeks after the second injection) will be used. To evaluate the long term effect of treatment with BoNT the different outcome measures assessed 16 months after the start of the study (approximately 1 year after the end of the trial) will be compared with baseline (t=0) and with the assessments at the end of the trial period (t=16 weeks)

7.1.3 Other study parameters (if applicable)

NA

7.2 Randomisation, blinding and treatment allocation

Patients will be randomized using a central web-based and validated computer program (ALEA) made available by the Clinical Research Unit(CRU) in the AMC. Randomisation will be stratified by type of psychogenic jerks (in extremity vs. abdominal jerks), using variable permuted blocks.

Randomisation lists will be handed by the CRU to the AMC pharmacy, who will safeguard the code. If needed, the randomization code can be broken by the pharmacy. Neither the subject, nor the investigator is informed about allocated therapy. Serious adverse events like life-threatening side-effects, will be an indication for breaking the code for that specific subject. Non-serious adverse events will be treated, but will not be an indication for breaking the randomization code

7.3 Study procedures

7.3.1 Neurological examination

During the study, patients will undergo systematic neurological examinations that will be videotaped. The neurological examination will take approximately half an hour. During the study, weakness will be examined using the Medical Research Counsil(MRC)-scale.
Psychiatric testing and evaluation of disability

- Patients will be asked to fill in some questionnaires concerning specific psychiatric conditions (mood disorders, anxiety and obsessive compulsive behaviour) and on the severity of disability during their visits. This will take approximately an hour per visit.
- Patients will participate in a psychiatric interview, the MINI-Plus, during their visits. On the first visit this interview will focus on current and previous DSM-IV diagnoses, while in the later visits only current diagnoses will be evaluated. During the first visit this will take approximately 1½ hour, in the later visits this will take approximately half an hour.
- The psychiatric interviews will be videotaped to be able to evaluate certain jerk characteristics for a longer period.

7.3.2 Interview

During their visits, patients will be interviewed by an independent investigator who will inquire about the effect of the treatment and whether patients would want to continue it considering all advantages and disadvantages. Furthermore the patients CGI-S and CGI-I will be evaluated. Patients will be asked if they think they were treated with BoNT or placebo during the trial phase of the study. Finally, the occurrence of adverse effects will be assessed. The entire interview will take approximately half an hour.

7.3.3 Duration of the visits

In total, the first visit will take approximately 5 hours, including the injection of BoNT or placebo. The following visits including assessments will take approximately 3 hours.

7.3.4 Scheme of the different assessments per visit

See also the time schedule of the study on page 17

Baseline (T = 0):

- Neurological examination, recorded on video
- Psychiatric interview, recorded on video
- Questionnaires (psychiatry, disability and tic assessment)
- CGI – severity by examiner (based on video) and patient
- Counting of the amount of jerks during 10 minutes of the psychiatric interview on video
- UMRS and PMD scale scores based on the recorded video during neurological examination
- fMRI scan (when participating in this sub-study)

T= 16 weeks:

- Neurological examination, recorded on video
- Psychiatric interview, recorded on video
- Questionnaires (psychiatry, disability and tic assessment)
- CGI – severity by examiner based on video neurological examination
- CGI-improvement relative to T = 0 by examiner based on video neurological examination
- Counting the amount of jerks during 10 minutes of the psychiatric interview on video
- UMRS and PMD scores based on the recorded video during neurological examination
- Interview (treatment effective, placebo or BoNT, CGI-S, CGI-I, VAS, adverse events)
- MRC weakness
- fMRI scan (when participating in this sub-study)

T = 16 months

- Neurological examination, recorded on video
- Psychiatric interview, recorded on video
- Questionnaires (psychiatry, disability and jerk assessment)
- CGI – severity by examiner based on video neurological examination
- CGI-improvement relative to T=0 and T=16 by examiner based on video neurological examination
- Counting the amount of jerks during 10 minutes of the psychiatric interview on video
- UMRS and PMD scale scores based on the recorded video during neurological examination
- Interview (treatment effective, CGI-S, CGI-I, adverse events)
- MRC weakness

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4.1 Specific criteria for withdrawal

NA

7.5 Replacement of individual subjects after withdrawal

Subjects will not be replaced after withdrawal.

7.6 Follow-up of subjects withdrawn from treatment

When patients withdraw from the study they will be asked to come to the Academic Medical Center one last time for neurological and psychiatric evaluation. Reason of withdrawal, if given, will be evaluated. These data will be used to evaluate the endpoints. If they refuse to come, their last observation is carried forward in the statistical analyses.

7.7 Premature termination of the study

As botulinum toxin is an established and safe therapy for other indications (see also section on safety), Functional magnetic resonance imaging is a non-invasive and safe procedure and is very commonly used in clinical practice and research. An interim analysis is not considered necessary

8. SAFETY REPORTING

8.1 Section 10 WMO event

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational drug or the experimental treatment. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.
SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.
A predefined list of AE's will be reported periodically instead of individually using the CCMO-module 'toetsingOnline'. AE's that will be listed and reported periodically are the following:

- local pain

- flu symptoms
- muscle weakness
- local haematomas

8.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to the investigational product related to any dose administrated. Unexpected adverse reactions are adverse reactions, of which nature, or severity, is not consistent with the applicable product information i.e. the summary of the product characteristics.
Using CCMO module 'Toetsing Online' all SUSAR's that could have consequences for the safety of the subjects involved in trial will be reported to the CCMO and central METC. The reporting will occur within 15 days after the investigator has first received information on the SAE. For fatal or life-threatening cases a preliminary report will be offered within 7 days followed by a complete report within 8 days.
The remaining SUSAR's are recorded in a overview list(line listing) that will be submitted once every 6 months to the METC. This line listing provides an overview of all SUSAR's concerning the trial medication, accompanied by a brief report highlighting the main points of concern.

8.2.2 Annual safety report

In addition to the expedited reporting of SUSARs, the investigator will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.2.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

8.3 Data Safety Monitoring Board

This study is considered a low risk trial. It is therefore decided not to institute a Data Safety Monitoring Board. An independent monitor from the CRU will monitor the data. In all trial subjects the informed consent forms and the in- and exclusion criteria will be checked. Source data verification will be performed in a sample of the population. The monitor also verifies whether all SAE's and SUSAR's are appropriately reported within the time frames required by GCP, the protocol, the ethics committee, and the applicable regulatory requirement(s).

9. STATISTICAL ANALYSIS

9.1 Descriptive statistics

Patient and clinical baseline characteristics will be summarized using simple descriptive statistics. Baseline values will consist of both categorical (e.g. sex, type of jerks, type of psychiatric conditions) and continuous variables (e.g. age, scores on questionnaires concerning neurological or psychiatric symptoms).

9.2 Univariate analysis

An intention to treat analysis will be performed with regard to the trial results. The difference in the proportions of patients reaching the primary outcome measure between the groups treated with BoNT and with placebo will be assessed using the $\chi 2$ statistic or Fisher's exact test, when appropriate. For the secondary outcome measures, proportional differences between the groups will be tested with the $\chi 2$ statistic. Difference in continuous secondary outcome measures will be assessed with the Students t-test or ANCOVA. For the long term effects, the assessments of individual patients at t=16 months will be compared with previous assessments using tests for paired data (paired t-test, McNemar's symmetry $\chi 2$ test for paired responses) or the mean difference between T = 16 months and T = 0. Finally, we will analyse repeated measures data using mixed effects models. In all analyses statistical uncertainties will be expressed in 95% confidence intervals.
Concerning the fMRI study the main study outcome measure is the difference in BOLD signal between scans of patients with psychogenic jerks before and after treatment with BoNT. Secondary outcome will be patterns of representations of external space and body scheme in patients compared to the patterns seen in healthy subjects. Another secondary outcome will be the performance of patients in the self-referenced and target-based finger movement task itself.

9.3 Multivariate analysis

If, despite randomisation, differences between important baseline-variables exist between groups allocated to placebo and to BoNT, multivariate regression analyses (logistic, linear, mixed effects, when appropriate) will be performed to adjust for imbalanced baseline variables.

9.4 Interim analysis

NA.

10 ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version of 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts. Data management, monitoring and reporting of the study will be performed in accordance with the ICH GCP guidelines. Technicians and data managers of the AMC Clinic Research Unit (CRU) will perform central data management using Oracle Clinical. Internet-based remote data capture will be used for entering, managing and validating data from the investigative sites. Oracle Clinical was designed to meet industry regulations, including: FDA 21CFR Part 11 Rule (1997), ICH; Good Clinical Practice: Consolidated Guideline (1997), and FDA Guidance for Industry "Computerized Systems Used In Clinical Trials" (1999).

10.2 Recruitment and consent

Patients will be recruited in several manners. First, the 20 patients with psychogenic jerks enrolled in an ongoing study focussing on the pathophysiology of jerky movement disorders will be evaluated for eligibility. Furthermore, suitable patients from our outpatient clinic will be asked to participate. Finally, movement disorder specialists from other clinics will be asked to refer suitable patients.

We will only ask those patients who did not object to being contacted for participation in clinical research. Possible subjects will receive an information letter and reply form by mail beforehand. Subjects who are willing possibly participate, are invited for an interview with the investigator at the hospital. Informed consent form will be signed by the subject in presence of the investigator. All patients that will be included in the BoNT treatment study at the UMC Groningen will be asked to participate in the fMRI study. Healthy controls will be recruited using flyers.

10.3 Objection by minors or incapacitated subjects

NA

10.4 Benefits and risks assessment, group relatedness

The different questionnaires used in our studies are considered to be mildly psychologically stressful. The medical intervention with BoNT is expected to be safe as BoNT has long been

used for numerous indications, mainly other movement disorders, with little side effects and few serious adverse events (see SPC).
A speculative potential risk factor concerns the underlying psychiatric co-morbidity in patients with psychogenic movement disorders. It is thought that motor symptoms in psychogenic movement disorders are an expression of underlying psychiatric symptoms/disorders.[3, 5] When motor symptoms disappear due to treatment with BoNT, patients may be faced with their underlying psychiatric illness or may develop other somatic symptoms to express their psychiatric disease. No previous studies are available to estimate the chance of this potential risk.
Psychogenic movement disorders gained very little attention from any discipline for a long time, especially with regard to research. Currently, neurologists more and more realise that psychogenic movement disorders are an important part of the movement disorder spectrum as well and feel the need for evidence based therapeutic options. This study will be one of the first randomized controlled trials in this population and the first studying the effect of botulinum toxin in patients with jerky movement disorders. The results may provide an entirely new treatment option in these patients.
Functional magnetic resonance imaging is a non-invasive and safe procedure and is very commonly used in clinical practice and research. This amendment to the study fits in with current studies at the department of Neurology at the AMC (MEC# 07/290). We can benefit from the experience in set-up and analysis from this study. Being able to perform prior and post treatment fMRI in this study will gain very relevant insights in effectiveness of the BoNT treatment, aswell as in pathophysiology and diagnostic possibilities of psychogenic jerks. And therefore will contribute largely to the BoNT study and to knowledge of the psychogenic jerks in general.

10.5 Compensation for injury

The investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The investigator (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;

2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives

NA

11 ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

Data will be handled confidentially and according to the Dutch Personal Data Protection Act. Personal data will be encoded by using a case record number. Paper data will be stored as Case Record Forms in a Trial Master File and coded by case record number. Digital data will be stored in a database and will also be coded by case record number. A separate file will contain the data to link the case record number to personal data. The key to the code will be safeguarded by the investigator who is responsible for the inclusion of patients. Data will be accessible to the investigator and collaborating investigators and to monitors, auditors, the accredited METC and other competent authorities. Data, video material and human material will be kept for a period of 15 years.

11.2 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

Two substantial amendments have been added so far:

- Amendment 1 startle reflex dd. 29-9-2011
- Amendment 2 fMRI dd. 8-8-2013
- Amendment 3 follow-up patients 22-12-2017
- Amendment 4 change principle investigator 17-1-2017

11.3 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers

of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.4 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

11.5 Public disclosure and publication policy

This trial will be registered at the Dutch Trial Register (Nederlands Trial Register; NTR). Any trial results will be made publically in peer-reviewed medical journals. Authors of the manuscripts will include the principal and collaborating investigators who have contributed to the trial.

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