Effectiveness of methylphenidate in children and adults with Smith Magenis syndrome and attention-deficit/hyperactivity disorder: An N-of-1 series

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON52697

Source
ToetsingOnline

Brief title
Methylphenidate for ADHD in Smith Magenis syndrome

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Developmental disorders NEC

Synonym
Smith Magenis syndrome; 17p11.2 deletion syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: 's Heeren Loo

Intervention

Keyword: ADHD, Methylphenidate, N-of-1, Smith Magenis syndrome

Outcome measures

Primary outcome

The primary outcome measure is the ADHD subscale of the Strengths and Difficulties Questionnaire (SDQ). The response options that are about *the recent past* will be substituted by *today*. The SDQ subscale has been psychometrically considered as a valid tool to measure behaviour of people with intellectual disabilities and applicable to both children and adults

Secondary outcome

Secondary outcome measures are the shortened version of the Emotion Dysregulation Inventory (EDI) reactivity index, Goal Attainment Scaling (GAS) and the Personal Questionnaire (PQ) to identify and measure the most obstructing symptoms experienced by participants. The response options that are about *the recent past* will be substituted by *today*. The EDI will be filled out daily at a certain time point by parents, caregivers, or patients themselves if capable. Participants will be contacted daily by the investigator to assess goals from GAS and possible side effects. Participants, parents and/or caregivers will keep a diary for scoring personal items from the PQ and possible side effects.

Study description

Background summary

Smith Magenis syndrome (SMs) is a rare genetic disorder characterised by complex pervasive and progressive behavioural and sleep disturbances with an estimated prevalence of 1:25.000 births. SMs is caused by a deletion on chromosome 17 (17p11.2) or linked to mutation in the RAI-1 gene that is encompassed by the common 17p11.2 microdeletion. Manifestations are distinctive physical features, developmental delay, cognitive impairment, and behavioural abnormalities including inappropriate or self-injurious, aggressive or stereotypic behaviour, and attention problems, hyperactivity, and impulsivity. Furthermore, infants experience feeding difficulties, failure to thrive, hypotonia, hyporeflexia, and sleep disturbances caused by an altered circadian rhythm. Treatment of SMs is complex due to the heterogeneity of symptoms. Currently, little research has been performed to inform effective treatments for manifestations of SMs.
Traditionally , treatment has focused on psycho-education and professional guidance for reducing symptoms and improving quality of life of both the person with SMs and its family. A retrospective study demonstrated that the vast majority of adults and children used at least one psychotropic medication, including stimulants, antidepressants, antipsychotics, sleep aids, mood stabilizers, alfa2 agonists, and benzodiazepines. No prospective studies on efficacy of psychotropic drugs have been performed. Considering the sleep disturbances, it is recommended in the 2008 NVAVG guideline to consider melatonin for circadian rhythm disturbances combined with metoprolol to reduce the inappropriate daytime melatonin secretion. Next to these sleep disturbances, an effective treatment should be examined for the remaining behavioural problems including symptoms of attention deficit (hyperactivity) disorder (AD(H)D). Patients with conduct problems, impulsivity and hyperactivity might benefit from treatment with a stimulant drug such as methylphenidate. As far as our knowledge goes, no studies have been performed to investigate the effectiveness of stimulants in SMs.
The randomized controlled trial (RCT) has conventionally been considered as the evidence for the effectiveness of an intervention. However, an RCT at population level is not feasible when it comes to rare disorders due to multi- and comorbidities. Reliable conclusions about the effectiveness of the intervention cannot be drawn due to matching issues. The n-of-1 trial is an alternative that has been considered as the most ideal study design to demonstrate causality of a symptomatic intervention in relatively stable disorders or with clear prediction of the progression at an individual level and with reversible outcome measures. The n-of-1 trial is a multiple cross-over placebo-controlled randomized study within an individual patient. N-of-1 trials are suitable in examining the efficacy of interventions in diverse and relatively small populations. Combining the results of several n-of-1 trials

yields information at a population level. N-of-1 trials enable within-subject comparisons, also applicable to similar conditions as the cross-over efficients, provide flexibility in the performance at an individual level, and therewith, demonstrate the relative efficacy at an individual level. Thus, n-of-1 trials regard the variability in treatment responses between individuals.
By using an n-of-1 series in patients with SMs, we will examine the efficacy of an intervention with methylphenidate on behaviour and relevant outcome measures. N-of-1 trials with methylphenidate for ADHD symptoms in SMs are suitable due to 1) ADHD has a chronic and stable clinical course; 2) methylphenidate has a rapid onset and termination of actions; and 3) caregivers seek for evidence for the use of stimulants because of biases and doubts. In this way, structured and evidence-based decisions can be made for an individual patient.

Study objective

The primary objective is to determine the efficacy of methylphenidate on ADHD symptoms in Smith Magenis syndrome.
The secondary objectives include the efficacy of methylphenidate on emotion dysregulation and specific goals that are important to the patient and its environment. Those personalized goals will be determined together with the participants using Goal Attainment Scaling and personal questionnaires, specifically paying attention to
A. Reduction of distraction, conduct problems, and impulsivity and hyperactivity;
B. Reduction of emotion dysregulation;
C. Minimization of burden for parents.

Study design

The n-of-1 series will consist of a double-blind randomized placebo-controlled multiple crossover trials within six individuals. The n-of-1 trial will consist of several cycles with each cycle containing a randomized order of one period of active treatment and one period of placebo treatment. One period lasts for seven days with a wash-out period of seven days with placebo after each period. The trial will start with a baseline measurement without any intervention followed by the consecutive periods of placebo or active intervention with methylphenidate. The total duration of a trial will be 12 to 13 weeks with a follow-up measurement three months after termination of the N-of-1 trial.

Intervention

Prior to the start of the trial during a clinical visit, the clinician will determine the dose of methylphenidate that is appropriate for the participant based on body weight and taking into account possible side effects.

Methylphenidate or the placebo will be administered twice a day at 8.00 am and 1.00 pm. In case of a child, the medication will be administered by the parents and caregivers.

Questionnaires will be filled out daily and participants will be contacted at the end of each period in order to assess personal goals, possible side effects and the expectation of the treatment.

Study burden and risks

No additional burden is expected as the design including blinded cross-over periods and the use of placebo for treating ADHD with methylphenidate is already Good Clinical Practice. However, the wash-out periods extend the time without active treatment. Furthermore, participants are required to fill in some questionnaires daily. On the other hand, every participant is exposed to the active treatment condition and an individual treatment decision will be retrieved in terms of evidence-based medicine. Therefore, we expect the benefits substantially outweighing the burden to be able to evaluate the effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

- A diagnosis of SMs confirmed with standard genetic testing (such as FISH test, microarray, WES-analysis).
- Meet DSM-5 criteria for ADHD, and diagnosed with ADHD by a multidisciplinary team consisting of an intellectual disability physician, a psychologist, and a psychiatrist.
- Minimum age of six years old.
- Presence of a patient*s caregiver for proxy-reports.

Exclusion criteria

- Presence of a contra-indication for treatment with methylphenidate.
- Planned general anaesthesia during the trial.
- Pregnancy.
- Breastfeeding females.
- Females of childbearing potential must be willing to use an effective method of contraception from the time consent is signed until 6 weeks after treatment discontinuation and inform the trial if pregnancy occurs.
- During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs.
- Current substance or alcohol abuse.
- Unable to swallow tablets / capsules.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-04-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Medikinet
Generic name:	Methylphenidate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-12-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-12-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2021
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2020-004053-76-NL
CCMO	NL73102.018.20