The effect of Lamotrigine on cognitive deficits associated with Neurofibromatosis type 1: a phase II randomized controlled multi-centre trial (NF1-EXCEL)

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The objective of this proposal is to determine the effect of Lamotrigine on cognitive functioning and neurophysiology in adolescents with NF1.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON47363

Source
ToetsingOnline

Brief title
NF1-EXCEL Effect of lamotrigine on cognition in NF1

Condition

- Neurological disorders congenital
- Cognitive and attention disorders and disturbances

Synonym
Neurofibromatosis type 1, Von Recklinghausen disease

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMw Priorities Medicine

Intervention

Keyword: Cognition Disorders, Drug therapy, Lamotrigine, Neurofibromatosis type 1

Outcome measures

Primary outcome

Cognitive functioning

- Performal intelligence (Wechsler Scales for Intelligence: 12 * 16 yrs:

WISC-III-NL; 17-18 yrs: WAIS).

Secondary outcome

Visual spatial learning efficacy

- Paired Associate Learning (from the CANTAB, Cambridge Neuropsychological Test

Automated Battery)

Attention

- Sustained Attention Dots (SADOTS, from the ANT, Amsterdam Neuropsychological

Tasks)

Fine motor coordination

- Grooved Pegboard Test

- Beery Visual Motor Intergration/ motor coordination task (Beery-VMI-6)

Attention problems

- Parent reported ADHD-questionnaire (AVL, ADHD Vragenlijst)

Executive function

- Behavior Rating Inventory of Executive Function (BRIEF-questionnaire)

Intracortical inhibition

- Short-interval Intracortical Inhibition (SICI), measured by paired pulse

stimulation

Cortical plasticity

- LTP-like plasticity, measured by paired associative stimulation (PAS)

Study description

Background summary

Neurofibromatosis type I (NF1; incidence 1:3000) is one of the most common monogenetic causes of cognitive disability. It is an autosomal dominant disorder, caused by mutations in the NF1 gene, and characterized by a wide variability of cutaneous manifestations, neurofibromas, and cognitive, social, motor and emotional problems. Despite the frequency of the disorder and the impact on daily life, there is currently no evidence-based treatment targeting the cognitive problems in NF1. The ENCORE-laboratory at Erasmus MC has recently shown that the cognitive deficits in Nf1 mice are caused by attenuated function of HCN-channels. In mice, Lamotrigine (LTG), an HCN-channel agonist, rescues the neuronal plasticity and learning deficits. Lamotrigine is approved to treat epilepsy and bipolar disorder, and is frequently used in children with NF1 to treat epilepsy. We hypothesize that Lamotrigine will decrease the over-inhibition in adolescents with NF1 and improve their cognitive functioning.

Study objective

The objective of this proposal is to determine the effect of Lamotrigine on cognitive functioning and neurophysiology in adolescents with NF1.

Study design

Phase II randomized double-blind placebo-controlled parallel group multi-centre trial

Intervention

Lamotrigine or placebo tablets: target dose of 2 x 100 mg/d.

Study burden and risks

Burden: Participants are required to take Lamotrigine or placebo tablets twice daily for 28 weeks. The total study duration from first inclusion visit till last outcome measurement will be 53 weeks. They have to keep a patient diary. Neuropsychological tests are assessed at baseline and after 6 months. Non-invasive neurophysiology measures are assessed at T=0 and T=10. The participants will visit the outpatient clinic four times: at T= -1 weeks, T=0 weeks, T=10 weeks and T=26 weeks. The visits at T=-1 weeks and T=26 weeks can also take place at the patient's home. The nature of the visit at T=18 weeks is always a home visit. During this visit compliance and adverse events will be monitored. Between the visits, parents and participants will be contacted by telephone at time points 4, 8, 14, 22 and 52. After T=26, there is a build-off phase of 2 weeks, after which there is an extra telephone contact at T=28. At T=52 weeks, participants receive a questionnaire to monitor off-phase attention problems. Finger prick for obtaining blood will be done at T=-1 week to assess renal function, liver values and complete blood count. Venipuncture will be done at T=10 to monitor blood lamotrigine levels, liver values and complete blood count. Additionally, at T=18 and T=26 weeks a finger prick for obtaining blood for lamotrigine plasma levels will be done. Total time investment by the participants for visits and testing will be +/- 13 hours.

Risks: Side-effects that are associated with Lamotrigine are known and manageable. (see SPC). Special attention is directed to the occurrence of skin rash, which will result in immediate withdrawal of study medication. There are no specific risks associated with outcome assessments. TMS, performed by trained personnel, is a non-invasive and safe method of measuring cortical inhibition and plasticity.

Benefit: If Lamotrigine has a positive effect on the cognition of adolescents with NF1, participants will have a direct benefit of participating in this trial. In addition, we would establish high-grade evidence for treatment of cognitive deficits in a vulnerable paediatric population.

Group relatedness: There are several reasons why we perform this study in children/adolescents instead of adults. These reasons are similar to trials previously performed in this population (MEC-2005-281 and MEC-2009-086). We expect the children*s/adolescent*s brain to have the highest ability to change (most *plastic*). Issues related to cognitive and behavioural deficits are most prominent in children/adolescents.
* The potential benefit of this study would directly apply to the study population.
* NF1-children/adolescents have a very characteristic profile of problems with school performance, behaviour and cognition. In contrast, at adult age, these problems have accumulated to a mild, broad range of cognitive deficits that are harder to quantify (probably because of adapting alternative problem-solving

strategies).
* From a practical point of view, we can only use some of the outcome measures (e.g. some of the attention tasks, parent-rated questionnaires) by testing children/adolescents.
* Again from a practical point of view, there are no specific outpatient clinics for adult NF1 patients and the patients that are available often suffer from complex somatic complications of NF1, reducing the generalizability of the results of this trial. In contrast, the outpatient clinics of the Sophia*s Children*s Hospital, UZ Leuven and KBO Kinderklinikum are representative of children with NF1 because the clinics are easily accessible and children remain in yearly follow-up after diagnosis.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Inclusion criteria

* NF1 patients with a genetically confirmed diagnosis
* Age 12-17.5 years at inclusion
* Oral and written informed consent by parents and assent from participants

Exclusion criteria

* Segmental NF1
* Severe hearing problems or deafness
* Severe visual problems or blindness
* Use of the following medication: fenytoïn, carbamazepine, fenobarbital, primidon, rifampicine, atazanavir/ritonavir, lopinavir/ritonavir, oxcarbazepine, topiramate, oral contraceptive pill (oestrogen and progestagen) and valproic acid during the last 3 months.
* Previous use of lamotrigine
* Previous allergic reactions to anti-epileptic drugs
* Epilepsy or epilepsy in the past
* Suicidal thoughts or behaviour
* Renal insufficiency
* Liver insufficiency
* Pregnancy
* Brain tumour or other brain pathology potentially influencing the outcome measures

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	31-10-2014
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lamotrigine
Generic name:	lamotrigine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-09-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-09-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-04-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-06-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	29-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2013-003405-26-NL
CCMO	NL44912.078.13