Effectiveness of methylphenidate in adults with phenylketonuria and attention-deficit/hyperactivity disorder: An N-of-1 series

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Primary Objective: To determine the effectiveness of methylphenidate in reduction of ADHD symptomatology, operationalized by personalized goals that are important to the patient and its environment, in individuals with late-diagnosed PKU. Secondary…

Ethical review	Approved WMO
Status	Will not start
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON50968

Source
ToetsingOnline

Brief title
MPH4PKU

Condition

- Metabolic and nutritional disorders congenital
- Inborn errors of metabolism
- Cognitive and attention disorders and disturbances

Synonym
PKU; PAH deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: subsidie AUMC Public Health

Intervention

Keyword: ADHD, Methylphenidate, N-of-1, Phenylketonuria (PKU)

Outcome measures

Primary outcome

The primary outcome measure is Goal Attainment Scaling.

Secondary outcome

Secondary outcome measures are 1) the Strengths and Difficulties Questionnaire,

2) Emotion Dysregulation Inventory (EDI), 3) the Personal Questionnaire (PQ) to

identify the three most obstructive symptoms experienced by participants, 4)

serum phenylalanine levels, and 5) adverse effects of methylphenidate.

Study description

Background summary

Phenylketonuria (PKU) is the most common inborn error of amino acid metabolism with a prevalence of 1 to 5 in 10.000 individuals. When dietary treatment is not started early in life, neurological abnormalities develop such as microcephaly, severe intellectual disability (ID), and impaired motor functioning, caused by prefrontal white matter pathology and impaired monoamine synthesis, including dopamine depletion. Psychiatric disorders often occur, such as attention-deficit/hyperactivity disorder (ADHD).
Since neonatal screening started in 1974, enabling an early dietary treatment, patients have near-normal cognitive outcomes. However, adults born before the start of newborn screening affected by ID and ADHD symptoms often present with behavioral problems due to their late or untreated PKU. This negatively impacts functioning and quality of life of the patient and their caregivers, and results in intensive, costly care.
PKU is an autosomal recessive disorder caused by defective activity of the enzyme phenylalanine hydroxylase (PAH) which converts Phe to tyrosine (Tyr), a

precursor of dopamine. Without treatment, Phe levels rise, Tyr is limited, and available Tyr competes with Phe to cross the blood-brain barrier, resulting in lower levels of Tyr available to synthesize dopamine. In idiopathic ADHD, decreased attention, restlessness, and impaired learning have been associated with decreased levels of extracellular frontal and striatal dopamine. In PKU, a molecular imaging study has suggested reduced striatal brain dopamine levels in PKU, supporting the hypothesis that executive functioning deficits in adult PKU may be associated with cerebral dopamine deficiency. The results of this study also suggested a relationship between the availability of striatal dopamine and degree of impulsivity, a major symptom of ADHD. Targeting the dopamine imbalance may improve ADHD symptoms and even a broader domain of functioning in late or untreated PKU.
Currently, behavioral problems in patients with late or untreated PKU are often treated with antipsychotic drugs targeting the dopamine system by blocking postsynaptic dopamine receptors, that may induce or aggravate parkinsonian features, and even worsen behavioral problems due to the already hypodopaminergic state. Instead, the first-line choice of treatment for ADHD features methylphenidate (MPH), a dopamine reuptake inhibitor, may be beneficial in PKU by raising brain dopamine availability. As currently no evidence is available, there is a call from caregivers as well as health care professionals for investigation of the effectiveness of MPH for ADHD symptoms.

The randomized controlled trial (RCT) is widely considered as the gold standard method for demonstrating the effectiveness of an intervention. However, an RCT at population level is significantly hampered when it comes to rare disorders due to comorbidities and rarity of the conditions. Hence, reliable conclusions about the effectiveness of the intervention cannot be clearly drawn due to matching issues.
The N-of-1 methodology has been considered an appropriate alternative study design to demonstrate causality of a symptomatic intervention in relatively stable disorders at an individual level and with reversible outcome measures. N-of-1 series are multiple cross-over placebo-controlled randomized trials within an individual patient. N-of-1 series are suitable in examining the effectiveness of interventions in diverse and relatively small populations. Combining the results of several N-of-1 trials potentially yields information that may be generalized at population level. N-of-1 trials enable within-subject comparisons as the crossover efficiently provides flexibility in the performance at an individual level, and therewith, demonstrate the relative effectiveness at an individual level. Thus, N-of-1 series take variability in treatment responses between individuals into account. Furthermore, multiple opportunities are provided to maximize adherence and care that is both patient-centered and evidence based. Overall, N-of-1 trials provide more rigorous evidence for treatment decisions at individual levels, closely succeed indications of causality between agent and effect as the key to studying interaction is replication, and enhance precision when these treatment effects are heterogeneous between individuals.
The value of N-of-1 trials is increasingly acknowledged, and applied to various

disorders including schizophrenia, cerebral palsy, traumatic brain injury, inflammatory bowel disease, cystic fibrosis, attention-deficit/hyperactivity disorder, obstructive airway diseases and migraine. Moreover, the N-of-1 design was used to evaluate cognitive and behavioural effects of methylphenidate in children with Williams syndrome concluding that methylphenidate is a useful adjunct in the treatment of some children with that syndrome.
We will examine the effectiveness of methylphenidate in patients with late-diagnosed PKU and ADHD symptoms, using an N-of-1 series. We consider that N-of-1 trials to study treatment effects of methylphenidate on ADHD symptoms are appropriate given that: 1) ADHD has a chronic and stable clinical course; 2) methylphenidate has a rapid onset and termination of actions; and 3) caregivers seek for confirmation 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 at short notice. In addition, little is known about the effectiveness of methylphenidate in patients with PKU with comorbid ADHD, as pharmacologically an increase of dopamine might have a beneficial effect. Our study results will provide crucial information about the effectiveness of methylphenidate for ADHD symptoms in PKU.

Study objective

Primary Objective: To determine the effectiveness of methylphenidate in reduction of ADHD symptomatology, operationalized by personalized goals that are important to the patient and its environment, in individuals with late-diagnosed PKU.

Secondary Objective(s): To determine the effect of methylphenidate on emotion dysregulation.

Study design

The N-of-1 series will consist of double-blind randomized placebo-controlled multiple crossover trials within at least five individuals. The individual N-of-1 trial will consist of three cycles each containing a randomized order of 4 seven-day periods: one active treatment (A), one placebo treatment (B), and two *washouts* with placebo following A and B. The trial will start with a baseline period of seven days without any intervention. A dose titration phase of six days will follow with a washout period of 2-6 weeks before starting the trial. The total duration of the trial will be up to 20 weeks with an additional open-label extension phase. Outcome measures will be assessed during the whole trial period at the end of interventional periods, and optionally during the open-label extension phase three months after the last intervention at the first follow-up measurement, and six months after the last intervention during the second and final follow-up measurement.

Intervention

Each participant receives multiple blocks consisting of an active treatment period of twice daily methylphenidate (doses based on titration phase) alternated with placebo and washout periods.

Study burden and risks

Blinded cross-over periods, the use of placebo and questionnaires are already common clinical practice for regular ADHD treatment with methylphenidate. For this study, a few clinical assessments and questionnaires are added to common clinical practice. Furthermore, the additional washout periods extend the time without active treatment. 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 to substantially outweigh the burden of participation.

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

- Minimum age of 18 years.
- A definite diagnosis of classical PKU according to well-established guidelines.
- Meet DSM-5 criteria for ADHD and diagnosed with ADHD by an expert multidisciplinary team consisting of an ID physician, a psychologist, and a psychiatrist.
- Presence of a patient*s caregiver for proxy-reports.

Exclusion criteria

- Unable to take and/or send in dried blood spots.
- Presence of ADHD in first- and second-degree relatives.
- Presence of a contra-indication for treatment with methylphenidate (e.g. cardiovascular disease).
- Planned surgery and/or general anaesthesia during the trial.
- Pregnancy.
- Breastfeeding (females).
- During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of one month of discontinuing those drugs.
- Current substance or alcohol abuse.
- Unable to swallow tablets / capsules.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Will not start

Enrollment:	5
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:	31-03-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-05-2021
Application type:	First submission
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	EUCTR2021-001174-29-NL

Register	ID
CCMO	NL77040.018.21

Study results

Date completed: 19-08-2024

Summary results
Trial never started