A randomized double blind, placebo-controlled study of fluoxetine in progressive multiple sclerosis (FLUOX-PMS)

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

Summary

ID

NL-OMON37668

Source
ToetsingOnline

Brief title
FLUOX-PMS

Condition

- Autoimmune disorders
- Demyelinating disorders

Synonym
progressive multiple sclerosis, slow degradation of the insulating layer of the nerve fibers

Research involving
Human

Sponsors and support

Primary sponsor: Prof. dr. J. de Keyser, Neurologie, UZ Brussel
Source(s) of monetary or material Support: MS anders Stichting

Intervention

Keyword: fluoxetine, progressive multiple sclerosis, randomized controlled trial

Outcome measures

Primary outcome

timed 25-Foot Walk (T25FW),

9-Hole Peg Test (9-HPT)

Secondary outcome

MRI: diffusion tensor imaging, global brain atrophy and T2 lesion load.

Cognition: MACFIMS, BDI, MFIS, HAI

Ambulation: Ambulation Index

Study description

Background summary

Based on the hypothesis that fluoxetine might suppress the antigen-presenting capacity of glial cells we performed a pilot study in patients with relapsing remitting MS and found that a daily dose of 20 mg tended to reduce the formation of new inflammatory lesions.

The progressive phase of MS reflects a poorly understood insidious axonal degeneration that is age related and independent of relapses. Currently available disease-modifying treatments, which act by modifying the immune response, are ineffective in progressive MS.

A mechanisms suspected to be involved in the widespread axonal degeneration in MS is a reduced axonal energy metabolism and axonal glutamate toxicity.Proton magnetic resonance spectroscopy has shown reduced levels of N-acetyl aspartate (NAA), which is a marker of axonal mitochondrial metabolism, and enhanced levels of glutamate 7 throughout the normal appearing white matter of the brain

in MS patients.

Astrocytes in MS are deficient in beta2 adrenergic receptors that are involved in (1) the release of brain derived neurotrophic factor, and (2) astrocytic glycogenolysis necessary for maintenance of sodium-dependent glutamate uptake, and the release of lactate, which is an energy source for axons.

Fluoxetine might reduce axonal loss underlying the progressive phase of MS because it stimulates glycogenolysis with lactate release and it enhances the production of brain-derived neurotrophic factor in rodent astrocyte cultures. We found that 2 weeks of treatment with fluoxetine (first week 20 mg/day and second week 40 mg/day) significantly improved the cerebral white matter NAA/creatine ratio, suggesting an improvement in axonal mitochondrial energy metabolism.

Study objective

We expect that in people with multiple sclerosis the processing of energy substances such as sugars (energy metabolism)i n the brains is not optimal . In our view this could explain the progressive deterioration of the disease.
Currently there are several therapeutic options for multiple sclerosis in which there are surges (so-called relapsing remitting multiple sclerosis). For the progressive forms without flares (so-called 'primary and secondary progressive multiple sclerosis'), there is no treatment that slows the progression.
If we could improve the energy metabolism by administering medication, we expect that this is a new way that might slow down the progressive deterioration of multiple sclerosis.
A number of times fluoxetine has been shown to improve this chemical energy metabolism in multiple sclerosis. With the present study, we will examine whether this also leads to long term slowing of the progressive phase.

Study design

randomized double blind, placebo-controlled study

Intervention

fluoxetine
placebo

Study burden and risks

Fluoxetine is a drug that used for over 20 years for the treatment of depression. However, the body of evidence that fluoxetine could have protective effects on nerve cellsis growing. As with all medication use, there is a risk of side effects, but these are well known and usually minor. Most common side

effects include gastrointestinal symptoms, drowsiness and sleepiness at the beginning of treatment, decreased libido, headache. The MRI brains hold no radiation burden. There is also no use of radioactive materials or contrast media.
It is possible that the study medication slows down the pathology of multiple sclerosis and could therefore be an advantage , but because this that advantage may not be guaranteed. For patients in the placebo group there is no direct effect on the expected disease course.

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

1.Signed written informed consent.
2.Either secondary or primary progressive MS according to the 2005 Revised McDonald

criteria.
3.Age 25-65 years.
4.EDSS at baseline of 3 - 6.5 points inclusive. Disability increased in the preceding year because of steady disease progression unrelated to relapses for at least 12 months.
5.Ability to be compliant with the schedule of protocol assessments.
6.For sexually active female patients with reproductive potential, use of reliable means of contraception.

Exclusion criteria

1.Pregnancy or lactation
2.Allergy to fluoxetine
3.Use of fluoxetine
4.Use of other antidepressants, unless they can be stopped for 2 months before starting with the study medication.
5.Contraindication for MRI (relative exclusion criterion because patients who have a contraindication are allowed to participate).
6.Major depression following the DSM-IV
7.Other neurologic, serious psychiatric or systemic disorders that could interfere with the assessments.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2012
Enrollment:	10

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	prozac
Generic name:	fluoxetine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-10-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-11-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-03-2014
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
Other	2011-003775-11 bij FAGG AFMPS
EudraCT	EUCTR2011-003775-11-NL
CCMO	NL40106.091.12