Long-term effects of SSRI treatment during (late) brain development in OCD patients: a retrospective MRI study.

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To report on (the age-dependency of) the long-term effect(s) of chronic SSRI treatment during adolescence or adulthood on the outgrowth and function of the 5-HT system, using state-of-the-art Magnetic Resonance Imaging (MRI) techniques and other,...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON37719

Source
ToetsingOnline

Brief title
ePOD-OCD

Condition

- Other condition
- Structural brain disorders
- Impulse control disorders NEC

Synonym
obsessive compulsive disorder

Health condition

neurotransmitter systeem (serotonine)

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,VENI beurs

Intervention

Keyword: brain development, long-term effects SSRIs, neuroimaging, serotonin

Outcome measures

Primary outcome

1) 5-HT system function with functional MRI before and after an i.v. challenge

with citalopram (5-HT challenge phMRI)

2) microarchitecture of 5-HT projections, using diffusion tensor imaging (DTI)

3) functional connectivity between several brain areas, using rs-fMRI

Secondary outcome

1) cognitive function related to dopaminergic function using neuropsychologic

tests and fMRI tasks (verbal memory, impulsivity, emotional processing)

2) confounding of genetic markers of the 5-HT system

3) cortisol sampling as indirect measure of 5-HT function

Study description

Background summary

50-90% of prescribed pediatric drugs have never been tested or licensed in children, only in adults. Approximately 100 million children in the European Union are prescribed off-label or unauthorized drugs and in doing so risk adverse reactions or do not respond to treatment at all. In fact, medication doses used in children are no more than *guestimates*. Clearly, there are potential dangers in assuming that children will have the same response to therapy as adults. SSRIs are the second most commonly prescribed psychotropic drugs in children and adolescents. In the pediatric population they are mainly prescribed for treatment of major depressive disorder (MDD) and anxiety disorders. In 2007 there were 8.500 patients under age 21 prescribed with SSRIs in the Netherlands alone. The rate of prescription is increasing over the past years (Stichting Farmaceutische Kengetallen), despite the controversy on their efficacy in treating childhood MDD. Although numerous trials have shown robust safety of SSRIs in adults, limited data is available on their effects on the maturing brain, and their efficacy in children and adolescents even debated (Hetrick et al., 2007). Animal studies have demonstrated that peri-adolescent pharmacological manipulations of extracellular serotonin (5-HT) concentrations ([5-HT]E) can lead to abnormal outgrowth of the 5-HT system (Azmitia et al., 1990; Shemer et al., 1991; Won et al., 2002). SSRIs increase [5-HT]E by blocking 5-HT transporters (SERT). Recently, MRI experiments of our group have shown that early chronic treatment with the SSRI fluoxetine in juvenile rats leads to an enhanced response to an acute 5-HT challenge in later life while adult-treated rats show a decreased response to a similar challenge. This clearly indicates the existence of age-dependent effects of SSRI treatment on 5-HT function (Klomp et al., 2012) and raises further concern about the use of SSRIs in children and adolescents and it is therefore vitally important to evaluate the long-term effects of SSRIs on the developing human brain.

Study objective

To report on (the age-dependency of) the long-term effect(s) of chronic SSRI treatment during adolescence or adulthood on the outgrowth and function of the 5-HT system, using state-of-the-art Magnetic Resonance Imaging (MRI) techniques and other, more indirect, measures of 5-HT function in a homogeneous group of OCD patients.

Study design

A pharmacological MRI (phMRI) study for assessment of 5-HT function and connectivity in the brain of adult subjects that have been previously treated with SSRIs during childhood/adolescence or adulthood (exposed group). Their outcome measures will be compared among each other and to an age and gender matched group suffering from OCD as well but who have not been treated with this type of medication (unexposed group). The (interaction) effect of age (of treatment) and treatment is investigated.

Study burden and risks

Burden of research day, total duration 4 hours:

- Neuropsychologic tests, saliva sampling for DNA and cortisol, questionnaires (about 1.5 hours)

- Insertion of intravenous line, administration of citalopram (7.5 mg) and twice drawing blood (max. 10ml each time)

- MRI scan (1 hour)

- 5 cortisol samples at home using cotton swabs (5x 2 minutes)

Risks:
Intravenous administration of a low dose of citalopram is generally well tolerated (See also section 5 of the study protocol) and does not contain any health risks for the participants. There will be minimal burden, which exists mainly of the insertion of the i.v. line.
Neuropsychologic tests, saliva sampling, questionnaires and the MRI scan do not add any risk and are considered to give minimal burden.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
1105 AZ, Amsterdam
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
1105 AZ, Amsterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) 20 subjects (male/ female) currently aged 23-45 years of age with (a history of) OCD and at least 4 months of treatment with an SSRI at or before 18 years of age, and medication free for at least one month.
2) 20 subjects (male/ female) currently aged 23-45 years of age with (a history of) OCD and at least 4 months of treatment with an SSRI at or after 23 years of age, and medication free for at least one month.
3) 20 subjects (male/ female) currently aged 23-45 years of age with (a history of) OCD and without any previous treatment with SSRIs or other antidepressants.

Exclusion criteria

-IQ < 70 (National Adult Reading Test (NART); Nelson, 1991).
-Alcohol and/or drug dependence according to DSM-IV criteria.
- Contraindications to MRI scanning (any kind of irremovable metal inside the body (including piercings, (large) tattoo*s, brackets, etc.), neurological disorders (e.g. epilepsy), claustrophobia).
- contraindications to citalopram use
- In case of female subjects: pregnancy

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	60
Type:	Anticipated

Ethics review

Approved WMO Date:	26-01-2012
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
CCMO	NL38988.018.11