Fluoxetine and the developing brain.

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Administration of fluoxetine during late brain development (adolescence), but not in adulthood, will result in abnormal outgrowth of the 5-HT system. This long-lasting disturbance of the 5-HT system may be visualized using MRI techniques and can...

Ethische beoordeling	Positief advies
Status	Werving tijdelijk gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON23639

Bron
NTR

Verkorte titel
ePOD_SSRI

Aandoening

Major depression/depressie, SSRI, fluoxetine, serotonine, development/ontwikkeling

Ondersteuning

Primaire sponsor: Academic Medical Center (AMC), Amsterdam
Overige ondersteuning: ZON-MW, The Netherlands Organization for Health Research and Development

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

1. phMRI: % change in citalopram induced BOLD signal from baseline;
2. DTI: % change in FA values from baseline.

Toelichting onderzoek

Achtergrond van het onderzoek

Country of recruitment: The Netherlands.

Background:

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, pilot experiments of our group have shown that early chronic treatment with
the SSRI fluoxetine results in a significant increase in prefrontal and hypothalamic SERT density in juvenile treated rats, but not in adult treated rats. These findings are in line with Wegerer et al. (1999), who has shown that this effect persists into adulthood, long after discontinuation of treatment with SSRIs. This raises 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.

Objectives of the study:

To report on the age-dependency of the effect(s) of the SSRI fluoxetine on the outgrowth of the serotonergic system using Magnetic Resonance Imaging (MRI) techniques.
To report on the age-dependency of fluoxetine on the outgrowth of the serotonergic system using functional
outcome measures (fMRI, neuropsychological test battery).
To report on the age-dependency of the effects of fluoxetine on the HPA-axis using cortisol measures (baseline and after challenge)

Study design:

A (pharmacological) MR imaging study for assessment of serotonergic function and connectivity in 16-week multicenter randomized, double-blind, placebo-controlled trial with fluoxetine in 80 adolescent-, and adult females suffering from MDD and/or anxiety disorder in which the effect of age is investigated before and after treatment. Patients will be stratified into two age groups: adolescents (12-14 years of age) and adults (23-40 years of age), and randomly assigned to receive a flexible dose of either fluoxetine or placebo, resulting in four groups consisting of 20 subjects each.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Since we study the effect of SSRI use on outgrowth of the serotonergic system in the maturing brain, it is essential to include individuals in which brain development is still ongoing, thus minors, and individuals in which brain development is considered to be complete, thus (young) adults.

Burden:

1. Intake studymedication (tablets) during 16 weeks daily (fluoxetine or placebo, doubelblind);

2. Screeningvisit and short exitinterview during which confronting or uneasy questions can be asked;

3. Two times collecting saliva samples (5) at home during one day and also during the assessment days (1
sample);

4. Two times assessment of neuropsychological tests and questionnaires (1 hour);

5. Two times MRI scan, including:

A. Starting i.v. line, administration of low-dose citalopram;

B. MRI scan, total duration 50 minuten.

Risks:

Side effects of fluoxetine. Since all patients are considered to be in need of pharmacotherapy, the risks of the fluoxetine treatment can be seen as part of standard practice and adds no extra risk to participation in this study.
Placebo-treatment. Recent studies have shown that there is a large placebo effect of 3 month

treatment with placebo en that the outcome of adolescents suffering from MDD treated with placebo versus fluoxetine is not statistically significant (Kennard et al, 2009). It was therefore concluded that placebo is an ethically acceptable control condition in terms of the potential for direct benefit, risk of harm from withholding active treatment, and availability and use of rescue procedures to minimize negative consequences. Patients can start medication directly after the study (after 19 weeks) and all adolescent patients receive additional cognitive behavioural therapy. The associated risk with study participation is therefore negligible, and the burden minimal.
Citalopram i.v.
Citalopram will be administered intravenously in a very low dose as a sort of contrast agent. Citalopram is the
only intravenously SSRI registered in the EU for treatment of severe depression with vital symptoms. In the Netherlands citalopram is the most prescribed antidepressant in children under 21 (although off-label, Stichting
Farmacologische Kengetallen, 2008). Intravenous form is given at the same dosage as oral form and side effects
are in the same range (mild and low-frequent; Kasper et al., 2002). These are: nausea (13%), headache (6%),
tremor (6%) and somnolence (25). Citalopram will be administered a two separate occasions in a very low dose
with 19 weeks interval. The associated risk is neglegible, and the burden minimal (mainly associated with the
intravenous puncture).
MRI, NPO, DNA and corticol measurement are without risks and burden is considered minimal.

Doel van het onderzoek

Administration of fluoxetine during late brain development (adolescence), but not in adulthood, will result in abnormal outgrowth of the 5-HT system. This long-lasting disturbance of the 5-HT system may be visualized using MRI techniques and can result in behavioral/cognitive abnormalities as well as hormonal disruptions.

Onderzoeksopzet

All assessments, except for the pharmacotherapy and genetic assay, will take place twice: once before start of study medication (baseline) and 19 weeks later (16 weeks treatment and 3 weeks wash-out). Besides this, control measurements will be obtained 3-4 times during pharmacotherapy.

Onderzoeksproduct en/of interventie

1. Random assignment to a flexible dose of fluoxetine or placebo drug treatment for 16 weeks, followed by a medication-free wash-out period of three weeks;

2. 3.0 Tesla MR imaging including diffusion tensor imaging (DTI), task-related functional MRI

(fMRI) and pharmacological MRI (phMRI) following 5-HT challenge with a low dose of the SSRI citalopram (5 or 7.5 mg, intravenous);

3. Assessment of a neuropsychological test battery and short questionnaires;

4. Collection of several saliva samples for cortisol measurement and a genetic assay for serotonin transporter gene promoter (5-HTTLPR) polymorphism.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Female outpatients, newly diagnosed with moderate to severe MDD and/or anxiety disorder (AD) (but not AD not otherwise specified (NOS) or adjustment disorder) as determined by a structured interview (DISC-IV; Ferdinand et al., 1998) or CIDI lifetime version 2.1 (WHO, 1992) by a (child and adolescent) psychiatrist. Rating scales: Children's Depression Rating scale-Revised in adolescents: (CDRS-R; Poznanski and Mokros, 1995) > 45, Children's Global Assessment Scale (CGAS; (Shaffer et al., 1983) <50. In adults: Hamilton Rating Scale for Depression (HRSD-17; Bech 1989) >18, Clinical Global Impression scale (CGI, Guy 1976) > 4, and or Hamilton anxiety scale (HAM-A; Hamilton)>20;

2. Subjects must exhibit stable dysphoria/depressed mood and/or anhedonia and/or

persistent anxiety symptoms for at least 2 weeks prior to enrolment and mood should be pervasive;

3. Also, already diagnosed MDD and AD adolescents unresponsive to CBT (but without prior pharmacotherapy treatment) will be included;

4. Age range is 12-14 or 23-40 years of age at the time of study entry.

Based on the above mentioned criteria, subjects will be enrolled in the study that are suffering from mild-to-severe MDD or AD that are in need of pharmacotherapy with an SSRI (fluoxetine) and therefore are eligible for participation in this 'acute treatment' study.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Estimated IQ < 70 (subtests Wechsler Intelligence Scale for Children-Revised (WISC-R); Wechsler, 1981 or National Adult Reading Test (NART); Nelson, 1991);

2. Other current Axis I psychiatric disorders like psychotic disorder, autistic disorder, ADHD and substance abuse, as defined in the DSM-IV;

3. Current or previous treatment with medications that influence the 5-HT system (for adults before 23 years of age): SSRIs, tricyclic antidepressants, triptans, MAO inhibitors Current or previous (ab)use (for adults before 23 years of age): of MDMA, amphetamine, methamphetamine, cocaine, heroine and LSD);

4. Prenatal use of SSRI by mothers of the patients;

5. Current treatment with CBT in adults;

6. Acute suicidality;

7. Contraindications to fluoxetine treatment (known hypersensitivity to one of the contents, use of other SSRIs or pimozide (Orap), thioridazine or monoamine oxidase inhibitors (MAOI) and Saint John's Wort);

8. Contraindications to MRI scanning (such as any kind of irremovable metal inside the body, claustrophobia, etc);

9. Pregnancy, breastfeeding or sexually active and not using/willing to use medically accepted means of contraception.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving tijdelijk gestopt
(Verwachte) startdatum:	01-02-2010
Aantal proefpersonen:	80
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	16-11-2009
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL1994
NTR-old	NTR2111
CCMO	NL26402.000.09
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A