SPACe 2 STAR : Safety and pharmacokinetics of antipsychotics in children 2. Studying TDM in An RCT

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This study has been transitioned to CTIS with ID 2024-511568-96-00 check the CTIS register for the current data. In SPACe 2 STAR, we aim to reach further, we will test whether application of TDM in clinical practice is indeed able to reduce the...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Developmental disorders NEC
Study type	Interventional

Summary

ID

NL-OMON56377

Source
ToetsingOnline

Brief title
SPACe 2 STAR

Condition

- Developmental disorders NEC

Synonym
autism, Autism spectrum disorder

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,ZonMw,Additional funding by stichting de Merel

Intervention

Keyword: Antipsychotic, Children, Pharmacokinetic, Therapeutic drug monitoring

Outcome measures

Primary outcome

Body mass index z-scores (BMI-Z), are measures of relative weight adjusted for child age and sex. to track relative weight status through the treatment.

Secondary outcome

Effectivity ABC: Aberrant Behaviour Checklist, a parental symptom checklist for assessing problem behaviour in children. The gold standard for measuring the effect of treatment on aggression and irritability in children with autism spectrum disorder.

Secondary safety parameters: Levels of glucose, cholesterol, lipoproteins and glucose; the hormones ghrelin, prolactin and leptin. AIMS: Abnormal Involuntary Movement Scale, a clinician administered observational scale aimed at detecting extrapyramidal side effects.

Mediators: DNA will be sampled to determine CYP 2D6 metaboliser status as well as single nucleotide polymorphisms*s of the P-glycoprotein blood-brain barrier pump, the dopamine receptor family (risperidone*s target), the dopamine transporter and catecholmethyltransferase (both involved in clearance of dopamine from the synaptic cleft) will be determined and investigated as potential moderator between drug through plasma levels and metabolic side effects.

In order to learn more about the mechanisms of weight gain associated with risperidone and aripiprazole use, we will administer a short questionnaire on

hunger, satiety and eating behaviour.

Study description

Background summary

An autism spectrum disorder (ASD) is characterised by impairments in social interaction, verbal and nonverbal communication, as well as by stereotypical patterns of behaviour and interests (American Psychiatric Association, 2013). Apart from these core symptoms, children and adolescents with ASD frequently display behaviour such as temper tantrums, aggression and self-harm (Lecavalier, 2006). Indeed, a Dutch study showed that almost half of the children and adolescents diagnosed with ASD suffered from a comorbid behavioural disorder as well (de Bruin, Ferdinand, Meester, de Nijs, & Verheij, 2007). Pharmacological interventions are an important part of the multimodal treatment of the comorbid behavioural problems. National and international guidelines recommend antipsychotics as agents of first choice (Werkgroep richtlijn autisme en aanverwante stoornissen bij kinderen en jeugdigen van de Nederlandse Vereniging voor Psychiatrie, 2009). Our research has shown that antipsychotic use in the Netherlands is high, with almost 10 out of every 1000 children and adolescents using antipsychotic medication (Kloosterboer, et al., 2018). Previously, few studies have adequately monitored long term antipsychotic safety profiles, though evidence indicates that extrapyramidal symptoms, cardiovascular and especially metabolic abnormalities are clinically relevant adverse effects in younger patients, with the individual agents differing in their propensity to induce side effects (Caccia, 2013; Cohen, Bonnot, Bodeau, Consoli, & Laurent, 2012). In atypical antipsychotics, the most prescribed class of antipsychotics in children and adolescents, metabolic abnormalities are of greater concern (Cohen, et al., 2012). In short term studies in children, weight gain amounted to an approximately 10% increase when compared to baseline (Aman, et al., 2002). In addition, antipsychotics have been reported to increase triglycerides by up to 45% (Meyer & Koro, 2004). Recently a large-scale epidemiological study showed that children receiving antipsychotic medication had a 3-fold increased risk of developing type 2 diabetes when compared to healthy controls (Bobo, et al., 2013). Moreover, childhood obesity is highly predictive of adulthood obesity (Ogden, 2007) and when childhood obesity persists in adulthood, these adults are at an even higher risk of type 2 diabetes, hypertension, dyslipidemia, and atherosclerosis compared to persons with adult-onset obesity (Juonala, 2011). In adults there is evidence that therapeutic drug monitoring (TDM), i.e. the quantification of serum drug concentrations for dose optimization, can help in maximizing clinical efficacy while minimizing the risk of side effects (Hiemke, et al., 2011). Several studies have shown a relationship between risperidone and aripiprazole plasma levels and both clinical efficacy and extrapyramidal side

effects (Mauri et al. 2007; Kirschbaum et al. 2008). Previously however, no study had targeted the relation between drug plasma levels and indices of metabolic side effects in adults. In children and adolescents, only a few studies have been performed investigating the relationship between risperidone and aripiprazole, and response or side-effects. However, all of these studies have suboptimal study designs, as risperidone sampling was not performed under standardized protocols or a retrospective design was Children are a unique patient population because they not only differ physiologically and anatomically from adults, but also experience rapid changes in growth and development in the course of their childhood. That is why in the ZonMW GGG funded (2015) SPACe study we researched the relationship between drug plasma levels and metabolic side effects in children. To this end we first developed an analytic method that allowed us to quantify drug plasma levels using a dry blood spot method (DBS), where blood is obtained by means of a finger prick, and dried on a filter paper. This minimally invasive procedure, is well tolerated by children with ASD (Kloosterboer, et al., 2020). We successfully validated this method for the simultaneous quantification of risperidone and its metabolite 9-OH risperidone, and aripiprazole and its metabolite dehydroaripiprazole (Tron, 2017, Kloosterboer 2018). In 42 children who used risperidone and 23 children who used aripiprazole we developed population pharmacokinetic models. We used these models to show a clear relationship of risperidone and aripiprazole trough concentrations with weight gain over a 6 month period (Kloosterboer, 2020; Hermans, 2022 manuscript). From the data collected in SPACe 1, we defined optimal therapeutic plasma level windows for risperidone and aripiprazole. For risperidone, this window is between 3.5 and 7 µg/L with 5.25 µg/L as an optimal aim, as dosing towards the middle of the window will give the best chance of neither dosing over nor under the cut-off values. We found that at risperidone plasma levels above 7 µg/L one month after start of treatment, 87.5% of children had significant weight gain compared to 35% below this cut-off. 75% of children with a risperidone plasma level above 3.5 µg/L experienced significant therapeutic effect as measured with the Aberrant Behavior Checklist, while this was only the case for 36% of children with plasma levels below this cut-off. Based on retrospective data analysis, we found a therapeutic window for aripiprazole between 50 and 20 µg/L with 35 µg/L as an optimal aim. Plasma levels of aripiprazole above 50 µg/L showed significant weight gain after 1 year.

Study objective

This study has been transitioned to CTIS with ID 2024-511568-96-00 check the CTIS register for the current data.

In SPACe 2 STAR, we aim to reach further, we will test whether application of TDM in clinical practice is indeed able to reduce the number/severity of metabolic side effects, while retaining clinical effectiveness in children by means of a randomized controlled trial.

Study design

We will study the ability of TDM to reduce risperidone and aripiprazole induced side effects in a randomized control trial. Patients will be randomized to receive therapeutic drug monitoring or to care as usual (CAU), which does not include therapeutic drug monitoring. In the TDM arm, trough drug plasma levels will be measured by means of DBS at 4 and 10 weeks in steady state after start of antipsychotics treatment. Based on these plasma levels dosing advice will be given to the treating physicians. In the CAU arm plasma levels will be determined and no dosing recommendations given. Metabolic parameters (BMI, cholesterol, triglycerides) as well irritability/aggression symptom severity will be measured in both arms at baseline (before start of antipsychotic treatment), and 4, 10, 24 and 52 weeks later. With a follow-up time of one year, we will be able to determine the value of our intervention over a longer time period.

Intervention

Therapeutic drug monitoring (TDM) versus care as usual for children receiving risperidon or aripiprazole treatment.

Study burden and risks

All of the participants will be subjected to two additional fingerpricks. In addition they and/or their parents/caregivers will be asked to complete multiple questionnaires at five time points. The total extra time investment is estimated at 2,5 hours.The control group receive traditional care as usual.

Prescription of risperidone and aripiprazole is in accordance with national and international guidelines. Dosages will not exceed recommended dosages in these guidelines. There is extensive experience with risperidone and aripiprazole in routine clinical practice, we therefore do not expect many or new SUSARs. During the course of the treatment, we will monitor participants for changes in their health status which warrant dose reduction or termination of study treatment.

In the group receiving therapeutic drug monitoring and dosing advice children may receive a lower dose of the medicine than he / she would otherwise have received. This may lead to a delayed or lessened effect of risperidone and aripiprazole

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Age 6 to 18 years
AND Documented clinical diagnosis of autism spectrum disorder according to DSM IV or DSM V and comorbid behavioural problems
AND To start treatment with either risperidone or aripiprazole

Exclusion criteria

• Diabetes type I or II
• Congenital or acquired syndrome associated with changes in appetite, body weight or lipid profile (e.g. Prader Willi)
• Known history of Long QT syndrome (LQTS), cardiovascular disorders (myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), seizure disorder or oesophageal dysmotility
• Pregnancy

• Hypersensitivity to the active substance or to any of the excipients

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-03-2022
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Abilify
Generic name:	Aripiprazole
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Risperdal
Generic name:	Risperidone
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	08-06-2021

Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	07-04-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-05-2024
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
EU-CTR	CTIS2024-511568-96-00
EudraCT	EUCTR2020-005450-18-NL
CCMO	NL75882.078.20
Other	NL9824 - NCT05146245