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Study Identification

Unique Protocol ID:	ADHDstress
Brief Title:	Atomoxetine, Diurnal Profiles of Cortisol and α-amylase (ADHDstress)
Official Title:	Atomoxetine, Diurnal Profiles of Cortisol and α-amylase, Possible Biological Markers of Treatment Success
Secondary IDs:	

Study Status

Record Verification:	March 2017
Overall Status:	Recruiting
Study Start:	December 1, 2016 [Actual]
Primary Completion:	July 2018 [Anticipated]
Study Completion:	July 2018 [Anticipated]

Sponsor/Collaborators

Sponsor:	Praxis für kleine und grosse Leute
Responsible Party:	Principal Investigator Investigator: Martin Kammerer MD PhD [mkammerer] Official Title: Principal Investigator Affiliation: Praxis für kleine und grosse Leute
Collaborators:	Dr med Kurt von Siebenthal, Facharztpraxis für Pädiatrie, Winterthur, Switzerland Dr med Roland Kägi, Facharztpraxis für Pädiatrie, Zurich, Switzerland Dr med Corrado Garbazza, University of Basle, Switzerland Prof Vivette Glover, Imperial College London, UK Prof Alina Rodriguez, University of Lincoln, UK NOTE : "Dr med Kurt von Siebenthal, Facharztpraxis für Pädiatrie, Winterthur, Switzerland" has been asserted to be a valid organization name by Praxisfkgl. NOTE : "Dr med Roland Kägi, Facharztpraxis für Pädiatrie, Zurich, Switzerland" has been asserted to be a valid organization name by Praxisfkgl. NOTE : "Dr med Corrado Garbazza, University of Basle, Switzerland" has been asserted to be a valid organization name by Praxisfkgl. NOTE : "Prof Vivette Glover, Imperial College London, UK" has been asserted to be a valid organization name by Praxisfkgl. NOTE : "Prof Alina Rodriguez, University of Lincoln, UK" has been asserted to be a valid organization name by Praxisfkgl.

NOTE : Collaborators should have no more than 80 characters.

Oversight

U.S. FDA-regulated Drug:	Yes
U.S. FDA-regulated Device:	Yes
Unapproved/Uncleared Device:	No
Pediatric Postmarket Surveillance:	
Product Exported from U.S.:	Yes
IND/IDE Protocol:	No
Human Subjects Review:	Board Status: Approved Approval Number: KEK-ZH-Nr 2014-0245 Board Name: Kantonale Ethikkommission des Kanton Zürich Board Affiliation: Kantonale Verwaltung Zürich Phone: +41 43 259 79 70 Email: jana.amberg@kaz.zh.ch Address: Stampfenbachtrasse 121 CH 8090 Zürich Switzerland
Data Monitoring:	No
Plan to Share IPD:	No
FDA Regulated Intervention:	No

Study Description

Brief Summary:	Diurnal profiles of markers of the stress system are increasingly recognized as biomarkers of different kinds of depression and related states. They may also serve as markers of treatment success. However, this has not yet been studied in attention deficit disorder (ADHD). Especially, there is a paucity of research into the effect of ADHD medication on the diurnal profiles of cortisol as marker of the hypothalamic pituitary adrenal (HPA) system and of amylase as marker of the sympathetic adrenomedullar (SAM) system. The investigators propose a within subjects design with probands of a narrow age range (seven to ten years of age, same sex: boys only) in order to get first information about whether there is an effect of atomoxetine on these diurnal profiles of cortisol and amylase, what kind of effect it is and whether this effect is related to treatment success. The investigators control for motor activity by using actometer measurements.
Detailed Description:	Scientific and clinical Background There is very good evidence that the hypothalamic-pituitary- adrenal (HPA) axis is disturbed in depression. There is some evidence that the stress system also plays a role in attention deficit disorder (ADHD) (O'Connor, Heron et al. 2002). The investigators have shown that motor activity and attention deficit/ concentration are core symptoms of depression (Kammerer, Marks et al. 2009; Kammerer 2010). These symptoms are also the core symptoms of attention deficit hyperkinetic disorder (ADHD). There is increasing evidence that the diurnal variation of markers of the stress system (e.g. salivary cortisol for the hypothalamic pituitary adrenal (HPA) axis, salivary amylase for the

sympathetic adrenomedullar (SAM) axis) reveal characteristics of different types of depression, e.g. atypical depression (Tops, Riese et al. 2008), post partum depression (Tops, Riese et al. 2008; Taylor, Glover et al. 2009) and related states, e.g. posttraumatic stress disorder (PTSD) (Wessa, Rohleder et al. 2006) and chronic fatigue syndrome (Roberts, Wessely et al. 2004).

There is some evidence that the saliva cortisol levels and the cortisol awakening rise may be markers of treatment success (Roberts, Papadopoulos et al. 2009). Salivary cortisol and salivary amylase are easy to study as only saliva is needed. (Clow, Hucklebridge et al.; Kirschbaum and Hellhammer 1989; O'Donnell, Kammerer et al. 2009). The investigators have tested saliva amylase, found it to be robust and a useful marker for the function of the SAM system (O'Donnell, Kammerer et al. 2009).

However there is still insufficient research into the diurnal profile of cortisol and amylase with children suffering from ADHD. This causes a serious lack of information for both clinical child and adolescent psychiatry and paediatrics as well as for the research community.

Atomoxetine was originally developed to be used as an antidepressant and shows an excellent therapeutic effect on attention deficit and hyperactivity with children suffering from ADHD. It is a selective re-uptake inhibitor of noradrenaline from the synaptic cavity (NARI).

Research into the possible effect of medication with Atomoxetine in children on their diurnal profile of cortisol and amylase has – to the investigators' best knowledge - not been carried out. The possible effect on the diurnal profile of cortisol and amylase could be linked to treatment success in general and to improvement of individual symptoms of ADHD. It may also contribute to a better understanding of possible side effects.

The investigators propose a study – with a within subjects design - with five times daily saliva collection on two consecutive weekdays before medication commences. Measurements will be repeated in weeks one, four and twelve of medication of Atomoxetine. Additional questionnaire data collection (Conners, CBCL) and, if feasible, testing (KI TAP) will be carried out.

The study will provide insight into possible effects of the compound (Atomoxetine) on the stress system. It may identify easily measurable biological markers of treatment success, and provide research into possible markers of respondents and non respondents. The investigators control for motor activity by using actometers.

Hypotheses to be tested

1. The cortisol awakening reaction (CAR) will be significantly different before, immediately after and four and twelve weeks after begin of the mediation of Atomoxetine with boys aged seven to ten.
2. The overall cortisol level will be different at the three measurement time points from each other.
3. The diurnal profile of salivary amylase and the overall amylase level will be significantly different from each other at the three measurement time points.
4. There will be a group effect regarding the diurnal profile distinguishing responders to Atomoxetine (response=50%reduction of symptoms) from non responders.

Plan of Research

Ethical approval

The protocol has obtained approval by the relevant ethical committees prior to begin of the study.

Location

A network of paediatrician’s n Switzerland.

Subjects and tests

Eligibility criteria:

Boys are eligible, age seven to ten, without comorbid psychiatric and/or somatic condition for whom the responsible paediatrician and/or child psychiatrist gives the indication for treatment with Atomoxetine and parents follow this advice. In order to exclude effects of prior psycho pharmacotherapy psychotropic drug naive boys only will be chosen. The diurnal variation seems to change as children grow older (unpublished observations of our group). Therefore, we want to try to get a sample that is as homogenous as possible.

Exclusion criteria:

Suicidal risk, depression, history of epileptic seizures, co morbid psychiatric or somatic conditions, history of psychotropic medication.

Power:

With an n=50 the investigators expect a power of 80% at 5 % significance and an SD of 0.6. In our study of postpartum depression (Taylor et al, 2009) we reached significant differences between the groups with an n= 30 and an n=21.

Sample:

• 50 boys, seven to ten yours of age, with clinical diagnosis of ADHD (ICD 10 or DSMV)

Measurements

Biological measures

Method for measurement of saliva cortisol and saliva amylase:

The same methodology will be applied as in (O'Donnell, Kammerer et al. 2009; Taylor, Glover et al. 2009) Actometer measurements using actometers provided by www.resmed.ch

Psychological measures

Assessment tools for quantifying ADHD symptoms will include the German version of the CPRS-R:L (Conners 1998; Conners, Sitarenios et al. 1998; Conners, Sitarenios et al. 1998), the CTRS-R:L (Conners, Sitarenios et al. 1998), the SDQ, parent and teacher version (Goodman 1997), Achenbach, T.M., & Rescorla, L. A. (2001). Manual for the ASEBA School-Age Forms and Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, and Families. ISBN 0-938565-73-7

Conditions

Conditions:	ADHD
Keywords:	ADHD, cortisol, α-amylase, actometer

Study Design

Study Type:	Observational
Observational Study Model:	Case-Only
Time Perspective:	Prospective

Biospecimen Retention:	Samples Without DNA
Biospecimen Description:	Saliva samples
Enrollment:	50 [Anticipated]
Number of Groups/Cohorts:	1

Groups and Interventions

Intervention Details:

Drug: Medication Other
medication of atomoxetine

Other Names:

- atomoxetine

Device: motor measurement and saliva collection
motor measurement by actometer and saliva collection for measurement of saliva cortisol and saliva alpha amylase

Outcome Measures

Primary Outcome Measure:

1. saliva cortisol
   diurnal profile of saliva cortisol and saliva alpha amylase

   [Time Frame: 13 weeks]

Eligibility

Study Population:	Boys are eligible, age seven to ten, dignosed with ADHD, without comorbid psychiatric and/or somatic condition for whom the responsible paediatrician and/or child psychiatrist gives the indication for treatment with atomoxetine and the parents accept their advice.
Sampling Method:	Non-Probability Sample
Minimum Age:	7 Years
Maximum Age:	10 Years
Sex:	Male
Gender Based:	Yes Boys only
Accepts Healthy Volunteers:	Yes
Criteria:	Inclusion Criteria: Boys are eligible, age seven to ten, without comorbid psychiatric and/or somatic condition for whom the responsible paediatrician and/or child psychiatrist gives the indication for treatment with atomoxetine. Exclusion Criteria: Suicidal risk, depression, history of epileptic seizures, comorbid psychiatric or somatic conditions, history of psychotropic medication.

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Links:

Study Data/Documents: