PROTOKOL

Testing a Cognitive Behavioural Therapy program for Anxiety in Teenagers on the Autism Spectrum: A feasibility study

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Objectives

The primary objective is to investigate the feasibility of a newly developed manualised group Cognitive Behavioural Therapy (CBT) programme for anxiety in teenagers (aged 13-17 years) with Autism Spectrum Disorder (ASD). Our aim is to focus primarily on acceptability and compliance with the program with some investigation of treatment effects on anxiety diagnosis and anxiety symptoms.

Background

Autism spectrum disorders (ASD) include deviations and delays in the development of social interaction, communication patterns, restricted stereotyped and repetitive behaviours, and areas of interests (Szatmari, 2003). ASD conveys persisting negative effects on learning and development of independence in adulthood (Howlin, Goode, Hutton, & Rutter, 2004).

The prevalence of ASD has increased markedly over the last three decades (Atladottir et al., 2015; Bertrand et al., 2001; Fombonne, 2002; Scott, Baron-Cohen, Bolton, & Brayne, 2002; Wing & Potter, 2002) and is now thought to occur in about 6 cases per 1000. The average age of diagnosis is around 5.3 years (Parner, Schendel, & Thorsen, 2008) but resent studies show a large increase in incidence rates for ASD among teenagers (Jensen, Steinhausen, & Lauritsen, 2014). This increase is mainly identified for Asperger's syndrome since higher functioning children and teenagers with ASD are harder to identify before the beginning of adolescence where demands on social communication skills, flexibility and social interaction become more complex and thus surpass the ability of the young adult (Jensen et al., 2014).

Approximately half of teenagers diagnosed with ASD have a relatively poor psychosocial development into adulthood (Eaves & Ho, 2008) affecting work prospects, friendships and independence, and leaving them socially isolated and reliant on social, community and family care (Schall, Wehman, & Carr, 2014). Although outcome for adults with ASD has improved over recent years, many remain highly dependent on others for support (Howlin et al., 2004).

Co-morbid disorders in Individuals with ASD are common (Coleman, 2000; Ghaziuddin, 2005) and seem to have an even greater impact on the young person's life than the ASD itself (Coleman, 2000; Gillberg & Coleman, 1992). Thus, treatment of co-morbid disorders may potentially add considerably to the improvement of quality of life, general functioning, independence and development (Ghaziuddin, 2005).

Anxiety disorders (Brereton, Tonge, & Einfeld, 2006; Leyfer et al., 2006; Simonoff et al.,

2008; Steinhausen & Metzke, 2004) are some of the most prominent co-morbid disorders and are estimated to occur in 11-84% of individuals with ASD (Kreslins, Robertson, & Melville, 2015). Due to a unique interaction between anxiety and core ASD symptomology, the manifestation of anxiety in individuals with ASD differs in several ways from anxiety seen in typical developing youths. Anxiety in ASD is associated with more behavioural problems, such as social avoidance, repetitive behaviours and aggression (Kreslins et al., 2015).

Cognitive Behavioural Therapy (CBT) is shown to be very effective in the treatment of anxiety in neuro-typical children and teenagers (Higa-McMillan, Francis, Rith-Najarian, & Chorpita, 2016; Reynolds, Wilson, Austin, & Hooper, 2012). Children with co-morbid ASD, however, seem to respond less favourably to standard CBT programs (Rapee, 2003) and research shows that CBT programs specifically designed for children with ASD and co-morbid anxiety are highly efficacious in treating anxiety disorder (Chalfant, Rapee, & Carroll, 2007; Kilburn et al., 2020; Kreslins et al., 2015; Storch, Arnold, & Lewin, 2013; Sukhodolsky, Bloch, Panza, & Reichow, 2013) thereby reducing the co-morbid symptoms that otherwise untreated may lead to extra impairment in daily life skills. The majority of this evidence, however, is from studies with younger children and, to our knowledge, no study has so far evaluated the efficacy of such a program specifically developed for teenagers (Perihan et al., 2019).

Treatment of anxiety in teenagers with ASD is especially important since this is a vulnerable time of development. The teenage years are when social relationships become most important, youngsters start dating and get sexually interested, become more independent, and ideas and motivations are forming for future careers and work (Rapee et al., 2019). Autism Spectrum Disorder and co-morbid anxiety will interfere with many of these processes making this co-morbidity during the teenage period especially critical for long-term functioning, independence and ability to become self-sufficient (Volkmar, Reichow, & McPartland, 2014).

The CBT program aimed at younger children between 7 and 13 years of age – *'Cool Kids ASD Anxiety Program' 2nd Ed.* (Lyneham, Chalfant, Kilburn, & Rapee, 2018 (in print)) – has been examined in a randomized controlled trial (RCT) in a non-English-speaking general hospital setting. The study showed positive results in the efficacy and satisfaction of the program for younger children with ASD and anxiety (Kilburn et al., 2020). However, this program is not suitable for teenagers above the age of 12-13 years and thus, the efficacy on older teenagers and young adults are uncertain.

The child version – *'Cool Kids ASD Anxiety Program' 2nd Ed.* (Lyneham et al., 2018 (in print)) – uses hand puppets and animal cartoons and relates on full parental support. Issues dealt

with concerns mainly topics related to young children and the challenges they might face on a daily basis.

A program for older teenagers and young adults needs to target topics related to this age group where specific age-related challenges associated with this group of young people with ASD can be incorporated. Since social relationships are a main challenge for many young people with ASD and often courses them to withdraw from others and experience levels of social anxiety (Rapee et al., 2019), topics related to overcoming social difficulties and solving problems without close parental assistant are important to target in such a program. Further, targeting the co-morbid anxiety needs to be approached in an age-related manor in order to enhance involvement and participation in the program.

Since high functioning ASD is often not recognised before adolescence, the co-morbid difficulties might not have been dealt with earlier leaving these teenagers in need of disorder- and age-appropriate treatment programs. Thus, in order to secure the best possible developmental paths and future possibilities for teenagers with ASD, it is important that age-appropriate treatment manuals aimed at co-morbidities such as anxiety are developed and tested.

Method/Design

In cooperation with professor Ronald Rapee and clinic director Heidi Lyneham (the developers of the original Cool Kids programs) (Lyneham, Abbott, Wignall, & Rapee, 2003), we have developed an age-appropriate version of a manualised CBT group treatment suited to treat teenagers with ASD and co-morbid anxiety.

The program is in the process of being edited and finalised before translation and adaptation to Danish conditions.

Development of 'Chilled ASD Anxiety Program'

The *'Cool Kids ASD Anxiety Program'* was developed at the Centre for Emotional Health, Macquarie University, Australia specifically for children with ASD and co-morbid anxiety allowing for the difficulties that children with ASD experience (Lyneham et al., 2018 (in print)). The *'Cool Kids ASD Anxiety Program'* is aimed at children aged between 6 and 13 years and follows the original *'Cool Kids Anxiety Program'* (Lyneham et al., 2003) but with modifications relevant to autism. The cognitive work has been simplified, 2 relaxation techniques are introduced and in-session exposure is part of the planning together with simplification of the material with many prepared worksheets and

pictures. Further, two hand puppets are introduced in order to visualise and externalise the anxiety issues.

Using the child version of the ASD program as a template and some of the approaches in the '*Cool Kids (Chilled) Adolescent Anxiety Program'* program for neuro-typical teenagers, the PI Tina R. Kilburn has in collaboration with the Centre for Emotional Health, Macquarie University, Australia developed a version ('*Chilled ASD Anxiety Program'* (working title)) aimed at individuals above 13 years of age with ASD and co-morbid anxiety disorder. Further, in the development of the '*Chilled ASD Anxiety Program'* specific age-challenges (e.g. social difficulties, building confidence, problem solving ect.) associated with this group of young people with ASD have been incorporated. After joint editing and finalisation of the program it will be translated into Danish before being tried in the feasibility study.

Procedure

Study population

Thirty teenagers aged 13-17 years with an active ASD diagnosis and experiencing life interference anxiety symptoms will be eligible to participate in the study. Even though we expect the program to be beneficial for individuals older than 17 it will be more appropriate to recruit youngsters under the age of 18 (the legal age in Denmark) to enhance parents' participation.

Visitation

Recruitment will take place through information conveyed to general practitioners, different Regional Centres of Child and Adolescent Psychiatry, Community Care offices, the ASD association, and through media such as newspapers, journals and the internet.

After first contact the families will be contacted by the PI via email with the written information informing them about the project, the inclusion and exclusion criteria together with an invitation to a personal meeting conducted at a private interviewing room at the Aarhus University Hospital, Psychiatry, Department of Child and Adolescent Psychiatry, Research Unit or at the 'Joint Counselling for Children and Youths' (PPR) in Frederiksberg. In the mail and in the written information the right to bring an assessor at the meeting is explained. At the meeting, informal clinical screening of anxiety symptoms will be performed by way of interviewing the family about their daily life and experienced challenges, further information will be given and consent form signed by both parents with joint custody. If the young participant becomes of age (turns 18 years)

during the project time, he/she will have to sign a new personal consent form. The family is entitled to 48 hours reflection time before signing the concentform. Clinical psychologist with extensive knowledge of the project, ASD and anxiety will convey the oral information. The young people participating in the trial will receive the same oral information and be involved in the conversations with the parents about the trial. The young person's own statements will be given crucial importance.

The participants will receive a small token of gratitude in the form of a trip to the cinema for the family (DKK 500,-) for completing the treatment and answering all interviews and questionnaires throughout the project.

Inclusion

To be considered for enrolment into the project the teenagers will have to fulfil the diagnostic criteria for one or more anxiety diagnoses on the Anxiety Disorders Interview Schedule for DSM-IV: Parent & Child interview schedule (ADIS C/P) (Silverman & Albano 1996).

Further, a diagnosis of ASD according to the International Classification of Diseases, 10th edition (ICD 10) (WHO, 2010) by a Private Psychiatric Clinic or by one of the Regional Child and Adolescent Psychiatric Centres in Denmark should have been obtained. The ASD diagnosis may not later have been revoked by a psychiatrist. Participants will not be accepted into the project without accompanying documentation of their ASD diagnosis.

Exclusion

Exclusion criteria for entering the trial is low intellectual functioning (<70). Assessment of cognitive ability (IQ) has often been part of the investigation regarding a possible ASD diagnosis and will, with parental consent, be retrieved from the teenager's journal. However, if assessment of IQ is missing a short version of the Wechsler Intelligence Scale for Children (Wechsler, 2014) will be performed.

Further exclusion criteria are active psychosis, untreated hyperkinetic disorder, inability to speak Danish, or inability to leave the home, attend a group setting, or to meet for treatment caused by other psychiatric disorders.

Intervention

The group based manualised CBT intervention program '*Chilled ASD Anxiety Program'* (working title)

will be used. The program will be conducted in 10 sessions over approximately 13 weeks with a further booster session 3 months after treatment. The sessions are group based comprising five teenager and parent dyads and conducted weekly, with a one week break after sessions 3, 6, and 8 to allow participants time to implement strategies in daily life. Each session lasts 2 hours and includes time spent working with the teenagers alone, time with the parents alone and time with parents and teenagers together. The teenager and at least one parent will attend the groups. The main group therapist will be a psychologist certified or well experienced in the Cool Kids programs and the co-therapist will be a psychiatric nurse, educationalist, or master class or above psychologist. Further, a graduate psychologist will be involved as a practical helper.

Treatment integrity will be assed for teenager and parent dyads using questionnaires regarding number of sessions attended and homework compliance. All sessions will be videotaped and adherence to the manual will be assessed through observation of a random selection of 2 sessions out of the 10 sessions (20%) for each treatment group by a therapist who has not been involved in the treatment.

Participants will be encouraged not to seek other forms of treatment or change possible psychopharmacological medication during the trial period.

Measures

Feasibility

Post-treatment teenagers and parents will be asked to complete a questionnaire adapted from The Experience of Service Questionnaire (Attride-Sterling, 2002; Brown, Ford, Deighton, & Wolpert, 2014) measuring their satisfaction with the treatment. On a Likert scale they will be asked to rate positive statements as 'not true' (1), 'partly true' (2), or 'true' (3) and in an open section freely comment on their experience with the treatment.

Participant dropouts will be investigated together with the proportion of completed sessions, homework and questionnaires.

Therapists will complete a qualitative survey regarding satisfaction with contents, ease of conveying program, and suitability of the program to teenagers with ASD.

Following completion of the program a focus group comprising a sample of participating teens and separately parents will be established to discuss the strengths and weaknesses of the program.

Anxiety

Diagnosis of primary anxiety will be carried out using the Anxiety Disorders Interview Schedule for DSM-IV: Parent & Child interview schedule (ADIS/CP) (Silverman & Albano, 1996) for both teenagers and parents. ADIS/CP is a semi-structured interview with separate interviews for both teenager and parents designed to assess for current episodes of anxiety disorders, and to permit differential diagnosis among the anxiety disorders according to DSM-IV criteria.

The disorders are rated with a clinical severity rating (CSR) from 0 (no interference) to 8 (extreme interference) with severity ratings of 4 or above signifying the presence of a clinical disorder. The assessor's CSR score will be based on a combination of the parent and teenagers' CSR score plus a clinical evaluation of the extent of severity. The disorder with the most impairing diagnosis will be considered the primary anxiety diagnosis.

The ADIS/CP has demonstrated good-to-excellent 7–14 days test–retest reliability for the presence of specific anxiety diagnoses (Cohen's Kappa [κ] range for different diagnoses = 0.71–0.84 for children's interviews and 0.73–0.92 for parent's interviews) (Silverman, Saavedra, & Pina, 2001).

The ADIS/CP assessment will be performed by trained psychology students under supervision of a senior assessor. The interviewers will be blinded to the purpose of the study and will not assess the same participant more than once.

Additional anxiety assessments administered to teenagers and parents will be collected by the following questionnaires using an on-line data collection platform (REDCAP).

Spence Children's Anxiety Scale (SCAS) (Spence, 1998), is a questionnaire for teenagers and parents assessing the severity of anxiety symptoms broadly in line with the dimensions of anxiety disorder proposed the DSM-IV.

Children's Anxiety Life Inference Scale (CALIS) (Lyneham et al., 2013), is designed to assess life interference attributed to fears and worries from teenager and parent perspectives. The measure targets interference with the teenager's life and with the parent's/family's life.

Children's Automatic Thoughts Scale (CATS) (Schniering & Rapee, 2002), is a developmentally sensitive, general measure of negative self-statements across both internalizing and externalizing problems. Four separate subscales of cognitive content are assessed including physical threat, social threat, personal failure, and hostility.

Further, indications of ADHD will be assessed using the Attention Deficit/Hyperactive Disorder-Rating Scale (ADHD-RS) (DuPaul, Power, Anastopoulos, & Reid, 1998) and Teenagers' and parent's quality of life will, in addition, be investigated with The WHO-five Well-being Index (WHO-5) (Bech, 2004).

All measurements will be performed before baseline (Pre), after the intervention (Post) and at 3 months follow-up (Fu) (See Fig. 1).

Finally, demographic information will be obtained by questions concerning level of education, employment, household income, number of siblings etc. in addition to other background data such as previous treatment, special school attendance etc.

Analysis

This feasibility study is being conducted to assess the feasibility of the project in order to be able to scale to a bigger study. Our main aim is to learn about enrolment challenges, satisfaction of manuals and delivery of program, questionnaires and interview schedule. With this aim in mind we expect that a study population of 30 teenagers is a reasonable sample.

The satisfaction questionnaires will be analysed by calculating the percentage of 'not true', 'partly true', or 'true' answers for each of the questions while examples of both positive and negative comments will be reported including reasons for possible dropouts. Percentage of participant dropouts will be calculated together with the quantity of completed sessions and questionnaires. Extent of homework completed in preparation for each session will be calculated. Comments from therapists' survey and the focus group will be collected and reported as qualitative data.

Outcomes regarding changes in diagnostic status, severity of anxiety symptoms, life interference attributed to fears and worries, and teenagers' negative self-statements measured with ADIS/CP, SCAS, CALIS and CATS will be investigated. Mean scores (M) with standard deviations (SD) will be calculated Pre and Post-treatment and at FU for the above measurement followed by the use of Cohen's *d* for repeated measures to calculate within-group effect sizes at the different data points – pre to post-treatment and post-treatment to FU.

In addition, the overall percentage of teenagers free of primary anxiety disorder and free of all anxiety disorders will be calculated.

Statistical analyses will be conducted by the use of STATA (StataCorp, 2019) and the significance level will be set at P value of less than 0.05.

Timeline

January 2021 – June 2021

- Final translation and modification of treatment manual for teens, parents and therapists
- Request for Research Ethics Committee
- Notification to the Data Protection Agency
- Continuing funds applications
- Development of information material

July 2021 – September 2021

- Training of therapists
- Interviewing and inclusion of patients

October 2021 – June 2022

- Conducting feasibility study with 15 teenagers (see Fig. 1.)

July 2022 – December 2022

- Data analysis
- Publications

Collaborations

The project is instigated in a collaboration between Aarhus University Hospital, Psychiatry, Department of Child and Adolescent Psychiatry, Research Unit and Professor Ronald Rapee and clinic director Heidi Lyneham, Centre for Emotional Health, Macquarie University, Sydney, Australia. The existing successful cooperation with the Centre for the Psychological Treatment of Children and Adolescents (CEBU), Department of Psychology and Behavioural Science, Aarhus University, (Kilburn et al., 2020; Kilburn et al., 2018, 2019) is extended by agreement with Professor Mikael Thastum to include the above project.

Part of the intervention (approx. 3 additional groups) will take place at the 'Joint Counselling for Children and Youths' (PPR) in Frederiksberg. The recruiting, inclusion and data collection will be as described above and the therapist undertaking the treatment will be trained by the PI.

Plan for dissemination

All results, positive, negative or inconclusive, will be published in international, peer-reviewed psychiatric or psychological journals and be presented at relevant international conferences. National

interest associations, social medias and national media outlets will be informed together with Danish Regions and Local Authorities in order to update knowledge and enhance implementation. If the manualised treatment program appears beneficial the material will be available for purchase by professionals at CEBU, Department of Psychology and Behavioural Science, Aarhus University containing the names of the funding contributors.

Legal and financial aspects

Macquarie University will have copyright of the program abroad and a license to print and distribute the Danish version will be bestowed CEBU, Department of Psychology and Behavioural Science, Aarhus University who holds the sole Danish rights to other Danish Cool Kids treatment versions.

The study is funded by the TRYG Foundation with 999.664 DKK over a 2-year period. The funding will be used for remuneration of staff, materials, compensation, publication etc. and is payed to and administrated by Aarhus University Hospital, Psychiatry, Department of Child and Adolescent Psychiatry, Research Unit. The PI or other researches associated with this project have no economic affiliation with the TRYG Foundation.

Ethical consideration

The study is in the process of seeking approval from the relevant regional Ethics Committees.

In order to limit invasion in the family's lives with additional examinations it is decided to include teenagers already diagnosed with ASD.

Some participants might experience slightly elevated anxiety level when initiating the program due to confrontation of the problem. Information regarding this phenomenon will be offered at the first personal meeting between the family and the PI in order for them to contemplate a possible withdrawal from the study. Further, based on clinical judgement referral to relevant post trial treatment options will be conducted for non-responding participants (after follow-up).

The Data Protection Regulation and the Data Protection Act are complied with in connection with the processing of personal data in the project. The study is covered by the patient compensation act.

Perspectives

Resent findings provide evidence for the benefit of manualised CBT programs for children with ASD and co-morbid anxiety disorders (Perihan et al., 2019). In order to investigate whether the CBT program Cool Kids ASD can be adapted for teenagers, and positive findings regarding the efficacy of

the program in children (Chalfant et al., 2007; Kilburn et al., 2020; Kilburn et al., 2019), this study aims to determine the feasibility of the '*Chilled ASD Anxiety Program*'.

The literature provides evidence to suggest that structured, intense intervention like a manualised CBT group program not only will improve the main presenting difficulty (Danial & Wood, 2013; Kreslins et al., 2015; Storch et al., 2015; van Steensel & Bogels, 2015), but also other aspects of the participant's functioning such as peer relationships (Hirshfeld-Becker & Biederman, 2002).

Diminishing anxiety symptoms and maybe even symptoms of other co-morbid disorders may have great impact on the severity of the ASD and in addition, may aid in improving quality of life for the whole family while enhancing the teenager's prospects for independence.

However, to our knowledge standardized programs designed specifically for teenagers with ASD and anxiety are lacking and there are several clinical and practical difficulties in applying child-focussed programs in this age-group. In order to provide an efficient treatment, it is thus important to develop and investigate a manualised age appropriate program adapted to the specific challenges young people with ASD faces in their teenage years.

Manualized CBT manuals like the '*Chilled ASD anxiety program'* aimed at teenagers are of great need in order to facilitate the transportability of feasibility and efficacy to care settings where therapists may have less opportunity for extensive CBT training and expertise development. This, in turn, will improve implementation and provide age relevant treatment to a large sample of teenagers with ASD enhancing their possibility for future development, education and quality of life.

If results from this study are shown to be as positive as the results from the recently finished study investigating the efficacy of the Cool Kids ASD anxiety treatment program for younger children in a general hospital setting (Kilburn et al., 2020), a RCT study of this new '*Chilled ASD anxiety program'* may not be of urgent necessity before being available in clinical practice. However, long-term and in order to further establish efficacy of the program it will be required to conduct a larger RCT study.

Positive outcomes regarding satisfaction of the program for both families and therapists will, in addition, support the imminent implementation and use of the program in both child psychiatric and community settings even though a RCT is not yet completed.

The regular Cool Kids anxiety program has been tested on Danish children with good results (Arendt, Hougaard, & Thastum, 2016) and is now widely used in treatment of anxiety in neuro-typical children nationwide with CEBU successfully handling the distribution of manuals and courses in how to use the program. Subsequent the efficacy study (Kilburn et al., 2020), the Cool Kids ASD

anxiety treatment program for younger children is in the beginning of an implementation phase where distribution of manuals and access to courses for psychologists nationwide are being planned using the same set-up at CEBU. Depending on results from this feasibility study the '*Chilled ASD anxiety program'* will be administrated using the same established system.

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Figure 1. Flow diagram of participants through the study. The same diagram is relevant for the 3 groups in Frederiksberg.