

# Identifying what anxiety treatments are provided to neurodivergent children and young people and their outcomes in routine care: protocol for a data-driven electronic health records study (ACECAT-CRIS)

Huilin Chen<sup>1</sup>, Andrey Kormilitzin<sup>1,3</sup>, En-Nien Tu<sup>1</sup>, Jasmine Laing<sup>2</sup>, Siyu Zhou<sup>2</sup>, Gaia Scerif<sup>2</sup>, Cathy Creswell<sup>2,1\*</sup>

<sup>1</sup> Department of Psychiatry, University of Oxford

<sup>2</sup> Department of Experimental Psychology, University of Oxford

<sup>3</sup> Mathematical Institute, University of Oxford

## Lay Summary

Anxiety is a common problem for neurodivergent children and young people, however it can be very challenging to identify and to manage. In a national survey, many neurodivergent children and young people and their parents expressed their frustration with not getting the right support and not “being treated seriously until at a crisis point” (National Autistic Society, 2021). As a first step to understand what has been done and what else can be done to manage anxiety problems among neurodivergent children and young people, we will explore what interventions are currently offered by child and adolescent mental health services in a large NHS Trust to autistic children and young people who have problems with anxiety, and what the outcomes of these interventions are (if recorded). We will search the structural data field in current medical records and free-text clinical notes using a Natural Language Processing (NLP) model.

## Abstract

**Background:** Anxiety problems are more prominent in neurodivergent children and young people than in their neurotypical peers. Such high rates of comorbidity are important to recognise as this comorbidity is associated with a greater risk of adverse outcomes, including self-harm and suicidality, than either condition on its own. While both pharmacological and psychological treatments are often prescribed for anxiety problems in autistic children and young people, as well as in those with ADHD, the evidence base for their effectiveness has so far been inconclusive, and little is known about their treatment outcomes in routine care.

**Methods:** This study aims to explore the nature and outcomes of anxiety treatments for autistic children and young people and for those with ADHD using pseudonymised electronic health record data. Longitudinal trends of both structured records of diagnoses (as recorded by ICD-10 codes), demographic information, treatment team and free-text clinical notes on presenting problems, indication of treatments, treatment provision, treatment outcomes and side effects, will be extracted and analysed. Free-text clinical notes will be processed to extract key concepts of interest using Natural Language Processing.

**Discussion:** This study will explore what treatments are available for autistic children and young people, and those with ADHD, in routine care, as well as treatment outcomes. However, due to the nature

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\* Corresponding author: [cathy.creswell@psych.ox.ac.uk](mailto:cathy.creswell@psych.ox.ac.uk)

and availability of data, the findings will inevitably be limited in their generalisability, which we aim to address in future phases of research.

## Background

Globally, the prevalence of autism<sup>†</sup> and Attention Deficit Hyperactivity Disorders (ADHD)<sup>‡</sup> are approximately 1% (Zeidan et al, 2022) and 7.2% (Thomas et al, 2015) respectively. While epidemiological studies have focused on these conditions or ‘disorders’, it is important to note that in clinical, research, and advocacy approaches, there has been an important recent shift away from categorical deficit-only models and towards a focus on neurodiversity (i.e., variation in neurocognitive and emotional profiles of strengths and weaknesses, Mahdi et al, 2017; Pellicano et al, 2022). Cognitive and emotional differences associated with neurodiversity lead to unique strengths, but also challenges for neurodivergent individuals, especially when the external environment is incongruent with their intrinsic ways of thinking and feeling (Sonuga-Barke & Thapar 2021).

Anxiety problems are among the most common challenges faced by autistic children and young people, as well as those with ADHD. A recent meta-analysis (Lai et al, 2019) reported a pooled prevalence of 20% for anxiety problems in autistic individuals, which increased to 26% in clinical populations. Moreover, a high prevalence of anxiety problems seems to be relatively consistent throughout development, which indicates that childhood anxiety problems can have long-lasting effects on an autistic person’s adolescent and adult life. Similarly, anxiety comorbidity in children and young people with ADHD is reported to be around 27.5% - 37.9% (Mohammadi et al, 2021; Shea et al, 2014).

Anxiety problems are also linked to adverse outcomes in neurodiverse children and young people. Elevated levels of anxiety have been shown to be positively associated with the severity of core ADHD and autism symptoms (Tsang et al., 2015; Reimherr et al., 2017; Wood & Gadow, 2010; Rodgers et al, 2012). Such problems have also been shown to affect the autistic child or young person’s daily lives as well as their parents’ careers, whilst also being associated with greater risks of self-harm (in particular among higher-functioning autistic youth), compared to the general population (Stark, et al 2022, Jokiranta-Olkonieni et al, 2021). Likewise, anxiety problems moderate the relationship between core ADHD symptoms and suicidality (Levy et al, 2020).

The manifestation of anxiety in autism and ADHD has some similarities with, but also marked differences to, that in neurotypical populations. For example, triggers for anxiety include both 1) typical anxiety triggers (e.g. failure, Waldman, McPaul & Jahoda, 2023) and 2) neurodiversity-specific anxiety triggers (e.g. sensory over responsivity, Vasa et al, 2020). Theoretically, there are common underlying cognitive processes that account for anxiety in autistic, ADHD, as well as neurotypical children and young people. Across groups, negative biases, automatic negative thoughts, and

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<sup>† †</sup> The paper may use the terms “Autistic Spectrum Disorders” and “Attention Deficit Hyperactivity Disorders” to reflect the diagnostic labels used in the current diagnostic criteria (ICD-10 and DSM-5), given that the study aims to explore the provision of clinical services to the neurodiverse population. However, the authors acknowledge and endorse the fact that neurodiversity can be a natural part of individual differences, which does not necessarily equate to disorders.

physiological arousal can predict anxiety (Ollendick & White, 2012). Meanwhile, there are also other processes that are more specific to neurodiverse conditions. Under such condition-specific processes, some stimuli or contexts, which may be tolerable for neurotypical children and young people, can provoke anxiety for autistic children and young people, and for those with ADHD. For example, fear and worries related to differences in social communication and intolerance of uncertainty that can be elevated in the context of autism (Ollendick & White, 2012), and anxiety related to differences in cognitive processing, impaired inhibitory control and compromised responses to rewards that can be heightened in the context of ADHD (Schatz & Rostain, 2006).

Despite the clear importance and urgency of treating anxiety problems in autistic children and young people, as well as in those with ADHD, identification and management of anxiety problems can be complicated not only by the differences in anxiety profiles, but also by challenges including diagnostic overshadowing between anxiety and core symptoms of autism and ADHD, which can make their anxiety problems harder to identify (Kerns et al, 2015). In addition, some autistic children and adolescents, and those with ADHD may have an increased likelihood of experiencing alexithymia and emotional dysregulation, which may hinder the capability to communicate, locate and monitor emotional support needs (Kinnaird, Stewart & Tchanturia, 2019; Donfrancesco et al., 2013). Finally, professional support for emotional needs among neurodiverse populations is often lacking. A recent UK national survey (National Autistic Society, 2021) suggested that 80% of autistic individuals expressed frustrations at not receiving sufficient support at a young age. Even when professional support is available, the capacity of such support can often be very limited. According to NHS data collected in July 2022, 67.2% of children and young people with suspected autism, whose cases were open for at least 13 weeks, were yet to receive any professional contact (Digital NHS, 2023). To the best of our knowledge, there is no available aggregate national data on waiting times for support for children and young people with ADHD.

For those who do manage to access some support, while there are both pharmacological and psychological treatments for anxiety problems in children and young people, evidence on the effectiveness of such treatments for autistic children remains inconclusive (James et al, 2020; Perihan et al, 2020; Vasa et al, 2014), with a primary focus on short-term effects measured in randomised controlled trials and open-label studies (Sharma et al, 2021; Vasa et al, 2014). While CBT seems to produce moderate-to-large positive effects for autistic children and young people, as reported by clinician-administered assessment or parent reports (Sharma et al, 2021; James et al, 2020; Perihan et al, 2020), treatment response appears to be smaller compared to their neurotypical peers. The treatment effects also seem to vary with different sociodemographic variables (e.g. gender, Sharma et al, 2021). Similarly, some pharmacological treatments, like selective serotonin reuptake inhibitors (SSRIs), which are commonly prescribed for treating anxiety problems, have not consistently been found to be effective (Williams et al, 2013; Vasa et al, 2014). Some have even been reported to have moderate (e.g. reduced appetite and exacerbated irritability) to severe adverse effects (e.g. prolonged seizures) in the context of autism (Williams et al, 2013; Vasa et al, 2014), while others only have limited evidence suggesting small to moderate effects. Very few studies have looked at medium- to longer-term treatment effects of CBT in the context of autism (Sharma et al, 2021) and also the real-world treatment outcomes in autistic children and young people with anxiety problems.

Likewise, research findings on anxiety treatment effectiveness in children and adolescents with ADHD are limited and inconsistent. One study reported that those with comorbid anxiety and ADHD seemed

to benefit most from combined pharmacological and psychological treatments compared to different treatment modalities (CBT only, medication only or placebo, Halldorsdottir et al, 2015). However, in general, the participants with ADHD responded significantly poorer to CBT immediately post-treatment, with lower rates of remission, compared to neurotypical peers, however such differences seemed to wear off over time. Significant between-group differences have also not been found for combined treatment (medication and therapy), medication only treatment and placebo (Halldorsdottir et al., 2015). Again there has been limited evaluation of real world outcomes, however a review of patient medical records reported that a larger proportion of patients with comorbid ADHD and anxiety who received psychological treatments other than direct parent, teacher and child training improved after 1 year of treatment compared to those who received combined pharmacological (methylphenidate) and psychological treatments, or those who received pharmacological treatment alone. (Reale, et al, 2017). Taking these findings together, there are significant inconsistencies and gaps in current evidence on the longitudinal course of treatment provisions and related outcomes across treatment modalities, particularly in routine practice.

Successful provision of treatment in routine care is often a continuous process, embedded with the flexibility to change or adapt the formulation and/or treatment options/prescription as clinicians gather more information, rather than being a one-off, standalone decision. Additional treatments after initial treatment success are known to have significant effects on treatment responses and longitudinal outcomes in neurotypical children and young people with anxiety problems. For example, Phillip and colleagues (2002) found that having additional treatments was the only significant predictor for maintenance of desirable behavioural and symptom changes 7.4 years post-treatment in neurotypical anxious children and young people. However, care is often not provided consistently over time to a high standard. Retrospective medical bill review has reported that very few children and young people with anxiety problems have received a sufficient number of appointments for the treatments they were provided (psychological or pharmacological, Whiteside et al, 2016). While there is currently no evidence available for neurodiverse children and young people, it is crucial to build on evidence from established neurotypical research, and to examine treatment outcomes through a dynamic lens that will take into account the provision or lack of treatments, as well as how they may affect a neurodivergent individual, over time.

## **Aims and objectives**

This study aims to examine the nature and outcomes of current anxiety treatment options provided for autistic children and young people and children and young people with ADHD in a large NHS Trust in England. By doing so, we hope to depict a preliminary picture of strengths and potential gaps in current routine practice, which can thereby serve as the foundation of evidence based clinical improvement in the future.

In light of such aims, there are two main research questions:

1. Do autistic children and young people, and those with ADHD receive treatment for their anxiety problems?
  - 1.1. How many autistic children and young people, and those with ADHD, with reports or diagnosis of anxiety-related problems receive treatments?

- 1.2. For autistic children and young people, and those with ADHD, what is the proportion of treatments provided to target anxiety-related problems specifically, as opposed to targeting other problems?
- 1.3. What treatments are provided for anxiety-related problems in autistic children and young people, and those with ADHD?
  
2. How well do patients respond to treatment?
  - 2.1. How often are treatment outcomes recorded for anxiety treatments?
  - 2.2. What are the treatment outcomes for different treatments?

In addition, the study also aims to explore the following question:

3. What are the outcomes of different anxiety treatments (or treatment combinations) for children and young people with different diagnoses related to neurodiversity at different ages and different genders?

## **Methods**

### **Design**

Pseudonymised electronic health records (EHR) from the secondary mental health services in Oxford Health NHS Foundation Trust (OHFT) will be screened according to our inclusion and exclusion criteria through a combination of structured data selection and information extracted from free-text clinical notes using text mining and NLP methods. In later phases of the study, we will include more diverse data from mental health NHS Trusts in England.

### **Participants**

The study cohort has been identified by the Oxford Health NHS Trust CRIS team based on the following inclusion criteria:

For inclusion in the autism/ADHD group, children and young people (aged between 0 to 18 years old) will be included if they have a diagnosis of autism or attention deficit and hyperactivity disorder (ADHD), recorded with the following structured ICD-10 codes: i) childhood autism (F84.0); ii) atypical autism (F84.1); iii) Asperger Syndrome (F84.5); or iv) disturbance of activity and attention (F90.0); v) Hyperkinetic conduct disorder (F90.1); vi) Other hyperkinetic disorders (F90.8); vii) Hyperkinetic disorder, unspecified (F90.9).

Children and young people will also have either a diagnosis of an anxiety disorder or will have been reported to experience anxiety problems in free-text clinical notes, which will be identified by the NLP model.

For the purpose of the analyses, we include anxiety diagnoses recorded with the following ICD-10 codes: i) Agoraphobia (F40.0); ii) Social phobia (F 40.1); iii) Specific (isolated) phobia (F40.2); iv) Other

phobic anxiety disorders (F40.8); v) Phobic anxiety disorder, unspecified (F40.9); vi) Panic disorder (F41.0); vii) Generalised anxiety disorder (F41.1); viii) Mixed anxiety and depressive disorder (F41.2); ix) Other mixed anxiety disorder (F41.3); x) Other specified anxiety disorder (F41.8); xi) Anxiety disorder, unspecified (F41.9).

## **Intervention**

The study aims to look at all treatments that were delivered for anxiety problems in autistic children and young people, and in children and young people with ADHD. There are two main categories of treatments: 1) pharmacological treatments, such as antipsychotics, antidepressants etc; and 2) psychological treatments, including but not limited to cognitive behavioural therapy (CBT), family therapy, systemic therapy, counselling etc.

## **Comparison**

Not applicable.

## **Outcomes**

The primary outcomes for this study for each research questions include:

RQ1. Anxiety treatments provided:

1.1. Percentage of patients being offered treatment for anxiety problems out of the total number of patients who reported anxiety problems

1.2. Indication for treatment: Frequencies of different indication for which treatment is prescribed, and what proportion of indication is anxiety-related

1.3.1. Average frequency of the provision of each type of treatment or combination of treatment for anxiety problems across the study population.

1.3.2. Average frequency, dosage, and duration of different treatments offered to children and young people with autism and to children and young people with ADHD for anxiety problems.

RQ2. Treatment outcomes:

2.1. Rate of treatment response being recorded

2.2. Descriptive summary of treatment outcomes

RQ3. Descriptive temporal trends of the type, intensity/frequency, duration and/or dosage of treatment options being offered and their respective outcomes in autistic children and young people, as well as those with ADHD

The study also aims to explore the following secondary outcomes:

- 1) Descriptive summary of treatment outcomes for anxiety treatments for each treatment modality in autistic children and young people, and in children and young people with ADHD
- 2) Sub-group differences in the percentage of different treatments being offered and respective treatment outcomes:
  - 2.1. Different anxiety diagnosis (if recorded)
  - 2.2. Different neurodevelopmental diagnosis (as recorded by the ICD-10 codes)
  - 2.3 Different age range (infant:0-5 years old; children: 5-11 years old; adolescents: 11-18 years old)
  - 2.4. Different gender<sup>s</sup> (male, female, other)
  - 2.5. Different levels of verbal abilities (mild intellectual disabilities: 50~69 IQ; moderate: 36~49 IQ; severe: 20~35 IQ; profound <20 IQ; and medium-high functioning: IQ>70)

## **Analysis Plan**

### **Natural Language Processing**

In recent years, Natural Language Processing has demonstrated remarkable efficacy in extracting information from unstructured text. Named Entity Recognition (NER), one of the key information extraction techniques, is primarily aimed at identifying and classifying named entities or concepts of interest in text into predefined categories such as person names, medications, locations (Nadeau & Sekine, 2007). Recent advances in NLP have been driven by the advent of deep learning, especially the Transformer architecture (Vaswani et al., 2017), which has been the basis for popular models like BERT (Bidirectional Encoder Representations from Transformers) (Devlin et al., 2018) and GPT (Generative Pre-trained Transformer) (Radford et al., 2018). These models have set new benchmarks in a variety of NLP tasks, including NER, Relation Extraction and text generation and classification.

The development of an annotation schema is central to information extraction tasks as it sets the rules and guidelines for what information needs to be annotated in the text. Fort et al. (2016) discussed the importance of establishing explicit specifications for entity types, attributes, and relations to ensure that annotations are consistent and serve the intended purpose. When developing an annotation schema for information extraction, it is crucial to define the types of entities and concepts to be extracted, along with the attributes and relationships between them. The annotation process typically involves a team of human annotators who manually tag entities and concepts in a dataset. Training and providing guidelines to annotators is essential to ensure the consistency and quality of annotations (Hovy et al., 2006). Evaluation of the quality of annotations is an essential aspect that involves assessing the correctness and consistency of the annotated data. Inter-Annotator Agreement (IAA) metrics, such as Cohen's Kappa (Cohen, 1960) and Fleiss' Kappa (Fleiss, 1971), as well as F1-score

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The term "gender" here is used in line with the data field captured in the initial CRIS dataset. However, the authors acknowledge the differences between sex and gender and endorse gender fluidity as well as advocate for more inclusive gender research. When implementing this project, the authors will examine the data currently been recorded as "gender" more closely, and if, they pertain information closer related to "sex", we will raise and address this accordingly in our final manuscript.

(Manning et al., 2008) are standard metrics used to measure the consistency of annotations among multiple annotators. High IAA scores signify that the annotation schema is well-defined, and the annotators have a common understanding, thus contributing to the robustness and reliability of the information extraction model developed using the annotated data. The proposed information extraction (IE) and structuring pipeline will re-use and further extend our previously developed models (Kormilitzin, A. et al 2020, Senior, M. et al. 2020, Vaci, N. et al. 2020) as well as will make use of recent advances in clinical Large Language Models with parameter-efficient fine-tuning (Taylor, N. et al. 2022).

In this work, the annotation schema will include 1) symptoms of anxiety, and symptoms of other mental health problems; 2) treatment (pharmaceutical, non-pharmaceutical treatments as well as other professional support) related information; 3) indications for treatment (why certain treatments are prescribed/provided) and 4) the time each record was documented or when benchmark clinical activities took place. Annotation will be provided by a group of at least two independent researchers familiar with the field. Discrepancies will be resolved amongst the authors, if agreement is not achieved, further concerns will be discussed and resolved amongst at least two researchers and one public and patient involvement (PPI) contributor using the Delphi approach of consensus.

Training and evaluating an information extraction model with manually annotated data will involve several steps that ensure the model's efficiency and effectiveness. First, the annotated dataset will be randomly split in a stratified manner into - training, validation, and testing sets. The training set is used for training the model, the validation set for tuning the hyperparameters, and the testing set for evaluating the model's performance.

Using pre-trained Transformer architecture for sequence classification, the training dataset will be used to train the model. The validation set will be used to enhance the model's performance by finding the best set of hyperparameters (Snoek, Larochelle, & Adams, 2012). Finally, using the test set, the optimised model will be evaluate using a range of common evaluation metrics, such as: Precision, Recall, and F1-score (Manning et al., 2008). For sequence labelling tasks like Named Entity Recognition, additional metrics like micro and macro-averaging will be used. This provides an unbiased assessment of how the model is likely to perform on unseen data (Kohavi, 1995).

Furthermore, the errors made by the model will be analysed to gain insights into what types of mistakes are common and whether certain features or adjustments might improve performance (Raghu & Schmidt, 2020). If the model performance is not satisfactory, we will repeat the previous steps to iteratively re-train and further refine the model based on insights gained during the error analysis. Recently, it has been shown that using high-quality generated synthetic data may improve model performance.

Data will be recorded in the form of panel data to capture the temporal changes between treatment and treatment responses in a certain clinical case. (Please refer to a methodological paper in development for further details on model development).

## **Descriptive Summary Plan**



Primary outcomes 1-2 will be summarised descriptively and primary outcome 3. will be inspected visually, respectively for autistic children and young people, and those with ADHD.

For secondary outcome 1, treatment outcomes for different pharmacological therapies and for different psychological treatments of anxiety will be cross tabulated to identify possible subgroups of treatment and their associated outcomes, depending on data availability.

For secondary outcome 2 and 3, cross tabulation of prescriptions of different treatment options across different diagnoses, age range and gender will be conducted.

## **Discussion**

This study aims to explore the provision and outcomes of anxiety treatments in local routine care, with a specific focus on children and young people with common neurodiverse conditions. The findings will help pinpoint areas of strength in current practice as well as for future improvement, which can hopefully provide concrete insights for evidence-based clinical decision-making.

It is worth noting that there are several methodological limitations in this study: Firstly, given its nature as a secondary electronic health record dataset, the data available in the secondary mental health EHR database will inevitably be affected by the differences in ways which different clinicians or practitioners record cases, and some data may be missing due to technical or systematic issues. This means that, for problems that are not recorded in notes that are retrievable from the CRIS dataset (e.g. problems that are reported during visits in other clinical settings, for example, in emergency departments [ED]), no analysis can be conducted in this phase of the study. However, this limitation can potentially be partly addressed in later phases by applying for linkage data to the wider database. Secondly, given practical constraints, this study is only able to identify and analyse cases with clinical records of confirmed diagnosis of target neurodiverse condition. However, this will inevitably mean that our sample will underrepresent marginalised groups with limited or no access to treatment, as well as those whose cases may be open without any associated ICD-10 diagnoses, who may have reports of working diagnoses and/or problems in free-text. Moreover, as diagnostic overshadowing can go both ways, children and young people whose neurodevelopmental conditions may be overshadowed by their anxiety problems can also be missed, if their anxiety problems have not been formally diagnosed. In particular, girls with comorbid ADHD and anxiety are often found to be underdiagnosed with ADHD as their anxiety symptoms can overlap and overshadow inattentive presentation, commonly reported in this population (Quinn & Madhoo, 2014). Thirdly, this study primarily plans to utilise data from the Oxford Health NHS Foundation Trust, which only covers services in Oxfordshire, Buckinghamshire, Swindon, Wiltshire, Bath and North East Somerset. While there is a possibility of extending the project scope to include data from more trusts in various locations in the future, the findings from the initial phase will inevitably be limited in the diversity of its study population and thus generalisability.

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