Principal Investigator

First Name: Samuele
Last Name: Cortese
Degree: PhD, MBChB / MBBS
Primary Affiliation: University of Southampton
E-mail: samuele.cortese@soton.ac.uk
State or Province: Southampton
Country: United Kingdom

General Information

Key Personnel (other than PI):
First Name: Anneka
Last name: Tomlinson
Degree: BMBch, PhD, MSc (hons)
Primary Affiliation: Department of Psychiatry, University of Oxford
SCOPUS ID: Scopus Author ID: 56173326400
Requires Data Access? Yes

First Name: Zhenpeng
Last name: Li
Degree: PhD
Primary Affiliation: Department of Psychiatry, University of Oxford
SCOPUS ID: Scopus Author ID: 12771076300
Requires Data Access? Yes

First Name: Orestis
Last name: Efthimiou
Degree: PhD
Primary Affiliation: University of Bern
SCOPUS ID:
Requires Data Access? Yes

First Name: Andrea
Last name: Cipriani
Degree: MD, PhD
Primary Affiliation: University of Oxford
SCOPUS ID:
Requires Data Access? Yes

First Name: Christos
Last name: Christogiannis
Degree: MA/MS/MSc
Primary Affiliation: University of Southampton
SCOPUS ID:
Requires Data Access? Yes

First Name: Miguel
Last name: Garcia Argibay
Degree: PhD
Primary Affiliation: University of Southampton
SCOPUS ID:
Requires Data Access? Yes

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: NIHR
How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT00246220 - 42603ATT3002 - A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study To Evaluate the Safety And Efficacy Of Prolonged Release OROS Methylphenidate Hydrochloride (18, 36 and 72 mg/Day), With Open-Label Extension, In Adults With Attention Deficit/Hyperactivity Disorder
2. NCT00714688 - 42603ATT3013 - A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate Efficacy and Safety of Prolonged Release (PR) OROS Methylphenidate (54 and 72 mg/Day) in Adults With Attention Deficit/Hyperactivity Disorder
3. NCT00937040 - CR015058 (CONCERTA-ATT-3014) - A Placebo Controlled Double-Blind, Parallel Group, Individualizing Dosing Study Optimizing Treatment of Adults With Attention Deficit Hyperactivity Disorder to an Effective Response With OROS Methylphenidate
4. NCT00326391 - 02-159/CR011560 - A Placebo-Controlled, Double-Blind, Parallel-Group, Dose-Titration Study to Evaluate the Efficacy and Safety of CONCERTA (Methylphenidate HCl) Extended-release Tablets in Adults With Attention Deficit Hyperactivity Disorder at Doses of 36 mg, 54 mg, 72 mg, 90 mg, or 108 mg Per Day
5. NCT01323192 - JNS001-JPN-A01 - A Double-blind, Placebo-controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of JNS001 in Adults With Attention-Deficit/Hyperactivity Disorder at Doses of 18 mg, 36 mg, 54 mg, or 72 mg Per Day

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

PATIENCE Individual Patient DATa Network Meta-AnalysIs of the Efficacy aNd aCceptability of ADHD mEdication

Narrative Summary:

The analysis of aggregate data, although useful on its own, cannot estimate treatment effects for specific types of patients, i.e., it cannot account for important differences in characteristics of the patients that may significantly moderate treatment effects. PATIENCE, an Individual Patient Data Network Meta-Analysis (IPD-NMA), has been designed to use data from individual participants recruited in RCTs of ADHD medications, to enable more detailed and flexible analyses to be performed than those based on aggregate data. This will provide evidence to inform future clinical guidelines, support personalised approaches in the treatment of ADHD, and identify areas for further research.

Scientific Abstract:

BACKGROUND: Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent neurodevelopmental disorder which has been estimated to affect 5-7% of children and 2.5% of adults worldwide. It is characterised by inattention and/or hyperactivity-impulsivity, that lead to impairment in the family, classrooms, workplaces and social settings and can prevent individuals from maintaining relationships and reaching their full potential. A number of pharmacologic and non-pharmacologic treatments are available. A network meta-analysis (NMA) of published and unpublished data provided the most comprehensive evidence on the relative efficacy, safety and tolerability of pharmacological treatments across the lifespan at the group level.
NMA is a statistical method that uses data from multiple randomised controlled trials (RCTs) and aims to estimate the relative effects of all available treatments for a certain condition. Common applications of NMA use aggregate data and estimate average treatment effects, i.e., treatment effects at the group level. The analysis of aggregate data, although useful on its own, cannot estimate treatment effects for specific types of patients, i.e., it cannot account for important differences in characteristics of the patients that may significantly moderate treatment effects (e.g., previous exposure to medication, specific comorbidities and severity of symptoms).
OBJECTIVE: The overall objective of the IPD-NMA is the establishment of a hierarchy of the efficacy and acceptability/tolerability of the available pharmacological treatments for ADHD in sub-groups of children, adolescents or adults with particular clinical characteristics (see https://esm.ispm.unibe.ch/shinies/iCBT/ for an example). This will provide evidence to inform future clinical guidelines, support personalised approaches in the treatment of ADHD, and identify areas for further research.
DESIGN: An Individual Patient Data Network Meta-Analysis (IPD-NMA)
PARTICIPANTS: This NMA has been designed to use data from individual participants recruited in RCTs of ADHD medications, to enable more detailed and flexible analyses to be performed than those based on aggregate data.
MAIN OUTCOME MEASURES: Primary outcome is effacacy, secondary outcomes included tolerability and acceptability
STATISTICAL ANALYSIS: Two stage IPD-NMA

Brief Project Background and Statement of Project Significance:

For ADHD, as for many other disorders, clinicians, patients and parents/carers are faced with a range of possible medications to choose from. In the absence of evidence-based biomarkers and clinical predictors of response or adverse effects, currently treatment selection in the clinical practice often relies on trial-and-error [7]. This results in protracted periods of sub-optimal treatment until the drug that provides the optimum balance of efficacy and tolerability for an individual patient is identified. The most robust empirical evidence for the effects of treatments comes from RCTs. The results of these can be statistically combined in pairwise Meta-Analyses (MAs) to estimate the relative effects of two drugs (or one drug and placebo). When a range of treatment options are available, the utility of pairwise comparisons from MAs for selection of treatment is limited. NMAs overcome this limitation by comparing multiple treatments simultaneously in a single analysis to produce estimates of relative effects among all interventions [11]. In addition to including data on treatment comparisons provided directly from RCTs, NMAs also incorporate indirect information, obtained by

combining data from RCTs of different drugs evaluated against the same comparator. NMAs facilitate initial treatment selection by providing estimates of the extent to which patients with a clinical condition are likely to benefit from and/or not be harmed by a particular medication, as compared to a reference treatment (e.g., active drug or placebo).
However, NMA results based on aggregate data only estimate the average treatment effects, i.e., at the group level. Individual Patient Data Network Meta-Analyses (IPD-NMAs) analyse patient-level rather that group-level data. This type of analysis also has the capacity to provide estimates of the effects of medication on subgroups of patients with specific characteristics, such as previous exposure to medications, severity of symptoms and comorbidities which could moderate the effects of medications [12]. Additionally, an IPD-NMA has other advantages as compared to aggregate data NMAs, such as the ability to standardise analyses across different studies, harmonise the definition of outcomes, offset inadequate reporting of individual studies, and allow more accurate assessment of study quality [13] [14].
Data for IPD-NMAs may be obtained from trial investigators and sponsors, including pharmaceutical companies, either directly or via data-sharing repositories and platforms. In addition to published data, the datasets may include information on unreported outcomes, allowing additional comparisons to be made. The data collected are first re-examined and verified, and any discrepancies found are checked with authors. As well as re-analyses of data reported in trial publications, additional analyses can be performed on data not reported in trial publications, new hypotheses can be tested and data from participants excluded from the original analyses can be included [15].

Specific Aims of the Project:

AIM: To collect and analyse individual patient data (IPD) from published and unpublished RCTs of FDA-approved pharmacological treatments for ADHD in children, adolescents, and/or adults.
The overall objective of the IPD-NMA is the establishment of a hierarchy of the efficacy and acceptability/tolerability of the available pharmacological treatments for ADHD in sub-groups of children, adolescents or adults with particular clinical characteristics (see https://esm.ispm.unibe.ch/shinies/iCBT/ for an example). This will involve:
i. assessing pharmacological treatments in patients with ADHD, in terms of:
? overall efficacy on severity of ADHD core symptoms;
? tolerability (defined as dropouts due to adverse events);
? acceptability (defined as dropouts due to any cause);
? changes in body weight changes in blood pressure and in heart rate
? individual adverse events
ii. exploring interactions between treatment effects and potential moderators, to identify predictors of individual response to medication.
iii. re-analysing data to reduce clinical heterogeneity and network inconsistency, by controlling for any patient-level moderators identified.
iv. using the data to conduct time-to-event analyses.
v. IPD may include additional information compared to aggregate data

Study Design:

Meta-analysis (analysis of multiple trials together)

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

The selection of studies for the IPD-NMA follows the same criteria as in our previously published an aggregate data NMA [16], with the addition of including the newly FDA approved ADHD medication ? Viloxazine. The same study selection, inclusion and exclusion criteria are being used for this IPD NMA will be published in the study protocol.
Participants will include children (aged ?5 years and

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary outcome
Observer-rated efficacy: the endpoint scores for the severity of core symptoms of ADHD (combined score of inattention, hyperactivity and impulsivity) measured on validated ADHD rating scales will be used. For adults, efficacy will be based on ratings by clinicians and, for children and adolescents, ratings by clinicians and teachers will be used.
In the first instance we aim to use the same rating scale for all studies. If studies do not report scores from the same rating scale, we will convert different scores into one single score from the same rating scale, ADHD-RS, as done by Furukawa et al [18]. In order to convert, we need studies reporting scores from different rating scales for the same outcome. If we are able to convert everything into ADHD-RS, we will synthesise data as a mean difference.
If we are not able to convert different scales into ADHD-RS, we will keep the original scales and will do the analysis using the standardized mean difference. We will use the following hierarchy:
1. ADHD-RS
2. SNAP;
3. Conner?s rating scale (any version);
4. Other ADHD scales (e.g., SKAMP, PERMP).

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Please see table 1 attached for list of variables of interest

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Please see table 1 attached for list of variables of interest

Statistical Analysis Plan:

Our aim is to estimate the patient-specific effectiveness and safety of each drug, to facilitate a personalised choice of treatment. Our main hypothesis is that routinely collected patient-level covariates (such as disease and medication history, demographics, etc.) can be used to predict to some extent the effects of the various drugs on the outcomes of the individual patients, to guide a personalized choice of treatment. The overall target of our analysis is to estimate relative effects between all interventions with respect to [19] the endpoint ADHD symptom score, [20] the probability of dropping out of treatment and [21] the probability of specific side effects for a patient with certain characteristics after 12 weeks of treatment. To maximize the power to detect modifications of the drug effects according to patient characteristics, we opt to synthesise all data that becomes available. Consequently, our sample size will be the maximum available, subject to the responses from data owners. In cases of treatment switch during the randomised phase, patients will be analysed according to the drug they were initially allocated, i.e., following an intention-to-treat analysis.
It is very often the case that for some patients we do not have complete information on all the covariates of interest, or the outcomes. Analysing only patients with complete records will reduce our statistical power and may bias results, when outcomes are not missing completely at random. To retain patients with missing data in our analyses, we will create 10 multiply imputed datasets, while taking into account the stratification of patients in studies. This will be based on the missing at random assumption. We will use all covariates and outcomes for our imputation models. For implementation, we will use the jomo package in R [22].
Individual patient data network meta-analyses
We will employ a two stage IPD-NMA. At the first stage, we will analyse each study separately, using the 10 multiply imputed datasets [28]. We will fit a Bayesian model including linear interactions between treatment and a list of predefined suspected effect modifiers. These include: age, gender, weight, height, baseline ADHD score, comorbid psychiatric disorder and baseline quality of life score.

For binary covariates we will use a binomial likelihood, or, if deemed possible according to data availability, we will do a time-to-event analysis. To avoid overfitting and aiming to have better generalizability of our model, we will use a Bayesian LASSO prior distribution for all treatment-covariate interactions [29]. Next, the posterior estimates from all multiply imputed datasets will be combined into a final posterior distribution [30]. Using this distribution, we will summarize the study-specific estimates for average treatment effect and treatment-covariate interactions as well as their variance-covariance matrix from each study. Finally, we will synthesize the study-specific point estimates and variance covariance matrices across the whole network assuming consistency, using multivariate normal distributions. As in the analysis of aggregate data, we will assume a common heterogeneity parameter across the whole network. The final output of this analysis will be estimates of relative effects and 95% Credible Intervals for all treatment comparisons, for all levels of the effect modifiers. To facilitate the uptake of our IPD NMA results, we will build an online tool (for an example see https://esm.ispm.unibe.ch/shinies/iCBT/), where the estimates of our models will be used in conjunction with input regarding baseline patient characteristics to estimate patient-level relative effects regarding all interventions in the network.

Project Timeline:

12-36 months
Project start date: 01.01.2023
Data harmonisation: 6-12 months
Data analysis: 6 months
Data results reported back to YODA within 12 months of analysis completion

Dissemination Plan:

Publication of the results from each phase of the project in peer-reviewed, scientific journals and dissemination of the findings to the general audience via patient and public engagement. Potential journals include - Lancet Psychiatry, Lancet, JAMA.
We will ensure that the data providers are notified and have the opportunity to view the results before publication.

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