Principal Investigator

First Name: Yoshie
Last Name: Omachie
Degree: Ph. D.
Primary Affiliation: National Center of Neurology and Psychiatry
E-mail: morio@ncnp.go.jp
Phone number: +81-80-6862-3512
Address: Ogawa-Higashi-machi 4-1-1, Kodaira, Tokyo 187-8551, Japan
Ogawa-Higashi-machi 4-1-1
City: Kodaira
State or Province: Tokyo
Zip or Postal Code: 187-8551
Country: Japan

General Information

Key Personnel (in addition to PI):
First Name: Yoshie
Last name: Omachi
Degree: Ph. D. M.D.
Primary Affiliation: National Center of Neurology and Psychiatry

First Name: Yasunori
Last name: Morio
Degree: PhD
Primary Affiliation: National Center of Neurology and Psychiatry

First Name: Kazushi
Last name: Maruo
Degree: Ph. D
Primary Affiliation: Department of Biostatistics, Faculty of Medicine, University of Tsukuba

First Name: Hideki
Last name: Oi
Degree: Mr
Primary Affiliation: National Center of Neurology and Psychiatry

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: Japan Agency for Medical Research and Development
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_20.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_yoshie_omachi.pdf
https://yoda.yale.edu/system/files/coi_form_ho.pdf
https://yoda.yale.edu/system/files/coi_form_km.pdf

Certification

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

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. [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

Elucidation of the predictive factors for active and placebo drug response on social functioning and QOL in psychiatric illnesses

Narrative Summary:

This is an individual participant data (IPD) level meta-analysis for estimating factors leading to improve the quality of life (QOL) in the Japanese patient with Attention deficit hyperactivity disorder (ADHD) , in order to reduce the burden on them and their families. This research collects placebo-controlled clinical studies evaluated QOL, makes integrated data set and identifies factors leading to improve the QOL in the patient with ADHD by multiple logistic regression analyses.

Scientific Abstract:

1 Background
By accumulating data from placebo-controlled clinical trials or clinical studies of ADHD treatments, it seems possible to infer factors that determine active drug responsiveness, factors that amplify placebo response, or factors that improve the quality of life in ADHD patients.
2 Objective
The purpose of this research is to identify factors leading to improve the QOL in the patient with ADHD by collection of IPDs obtained in the Japanese placebo-controlled clinical studies measuring QOL in the past, and to estimate the relationship between the factors and the reactivity to treatment drugs and placebo.
3 Study Design
Database research using existing clinical trial / clinical research data
4 Participants
The placebo-controlled study in the Japanese patient with ADHD was searched and the following studies are identified: NCT00191295, NCT00962104, PMID: 32297719, NCT01323192 and NCT02305134.
5 Main Outcome Measure(s)
? Factor analysis of patient groups where the difference between active drug and placebo is likely to obtain
? Factor analysis of patient groups where it is difficult to make a difference between active drug and placebo
? Factor analysis of patient groups in which neither active drug nor placebo is effective
? Identification of the group having placebo response and analysis of its factors
6 Statistical Analysis.
Multiple logistic regression analyses will conduct to examine associations between drug or placebo responses.

Brief Project Background and Statement of Project Significance:

In the clinical trial of the therapeutic agents for psychiatric disorders, the severity of symptoms has been measured using an evaluation scale assessed by psychiatrists or psychologists, and the efficacy of the investigational drug has been confirmed. Various evaluation scales are also used in the clinical trials in the patient with ADHD.

However, in recent years, it has been pointed out that not only the objective symptom evaluation performed by psychiatrists and psychologists, but also the subjective evaluation of patients, functional improvement, and quality of life (QOL) evaluation are important.

From the results of meta-analysis of 4 clinical trials conducted in EU and US, atomoxetine improved not only an objective symptom measured by ADHD Rating Scale (ADHD-RS), but also some items of health-related quality of life (HRQoL). In patients with psychiatric disorders, it is often reported that there is a gap between the improvement of objective psychiatric symptoms and that of subjective symptoms, so the clinical significance of improving QOL becomes emphasized in determining the therapeutic effect. The correlation between the improvement of objective symptoms and that of QOL by atomoxetine treatment is not strong, and the factors that improve QOL should be elucidated.

As a method for estimating the factors, there is a meta-analysis that integrates data of clinical trials conducted by pharmaceutical companies and clinical studies conducted by academia in the past at the level of IPD. By accumulating data from placebo-controlled clinical trials or clinical studies of ADHD treatments, it seems possible to infer factors that determine active drug responsiveness, factors that amplify placebo response, or factors that improve the quality of life in ADHD patients.

Specific Aims of the Project:

The purpose of this research is to identify factors leading to improve the QOL in the patient with ADHD by collection of IPDs obtained in the Japanese placebo-controlled clinical studies evaluated QOL in the past, and to estimate the relationship between the factors and the reactivity to treatment drugs and placebo. One of the specific hypotheses to be evaluated in this study is whether the factors or variables leading to the improvement of QOL associate with baseline severity of symptom, age, age of onset, comorbid disorders, history of treatment, initial treatment response and so forth. Variables examined in this study will be based on those identified in original studies. However, if there are multiple variables that measure similar concepts, the study team will decide which variables to include in the models.

What is the purpose of the analysis being proposed? Please select all that apply.

Participant-level data meta-analysis
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

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

It has searched for identifying the placebo-controlled study in the patient with ADHD in Japan into the assessment reports of the approved drugs of the Pharmaceuticals and Medical Devices Agency and the two databases; Japan Pharmaceutical Information Center Clinical Trials Information (Japic CTI) and University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR). As a result, the following studies are identified.

Main Outcome Measure and how it will be categorized/defined for your study:

Main Outcome Measure(s)
? Factor analysis of patient groups where the difference between active drug and placebo is likely to obtain
? Factor analysis of patient groups where it is difficult to make a difference between active drug and placebo
? Factor analysis of patient groups in which neither active drug nor placebo is effective
? Identification of the group having placebo response and analysis of its factors
Statistical Analysis.
Multiple logistic regression analyses will conduct to examine associations between drug or placebo responses at the end of the treatment (e.g., a ? 25% improvement in the QOL score) and gender, age, baseline scores of the various scales of evaluation including QOL.

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

The purpose of this research is to identify factors leading to improve the QOL in the patient with ADHD by collection of IPDs obtained in the Japanese placebo-controlled clinical studies evaluated QOL in the past, and to estimate the relationship between the factors and the reactivity to treatment drugs and placebo. One of the specific hypotheses to be evaluated in this study is whether the factors or variables leading to the improvement of QOL associate with

baseline severity of symptom, age, age of onset, comorbid disorders, history of treatment, initial treatment response and so forth. Variables examined in this study will be based on those identified in original studies. However, if there are multiple variables that measure similar concepts, the study team will decide which variables to include in the models.

Statistical Analysis Plan:

The main objectives of this study are as follows:
A) To identify specific patient populations that are likely to show differences between an investigational agent and placebo, thereby facilitating the planning of efficient clinical studies in the future.
B) To identify specific patient populations that are unlikely to show differences between an investigational agent and placebo, thereby increasing the likelihood of successful clinical studies.
C) To identify specific patient populations in which both an investigational agent and placebo are unlikely to be effective, thereby discovering unmet medical needs.
D) To identify placebo-responsive populations, thereby identifying those populations that are truly responsive to an investigational agent by conducting biological studies (to separate the responsive group into an investigational agent-responsive group and a placebo-responsive group, thus allowing them to be analyzed separately).

To achieve these ultimate objectives, the following analyses will be performed. All analyses compare the investigational agent group and the placebo group, but do not directly compare different investigational agents in terms of effect or tolerability.

1 Study of responsiveness to placebo (predictors in the placebo group)
1.1 Although it is difficult to define the recovery or improvement of quality of life (QOL), responsiveness to treatment is basically assessed by a binary judgement (i.e., whether patients "responded" or "did not respond" to treatment). "Response" to the treatment will be defined based on the data collected.
1.2 Logistic random-effects regression models will be used to explain heterogeneity among studies, thereby enabling prediction of the response to placebo. A backward selection method with a p value of 0.15 as a cutoff will be used to identify candidate variables.
1.3 In addition, when necessary, machine learning approaches such as random forests will be used to identify predictors.
1.4 Cross-validation that eliminates studies one by one will be used to assess the external validity of the multivariate logistic regression models obtained. The Hosmer-Lemeshow statistic will be used as a calibration index and the C statistic will be used as a judgement index.
1.5 If a stable and efficient model is obtained, the placebo-responsive group can be distinguished from the group that is truly responsive to an investigational agent in the apparent responsive group.
2 Study of responsiveness to an investigational agent (interaction between the agent and background characteristics)
2.1 QOL scales used in original studies will be analyzed, and the possibility of conversion will be examined based on the data collected.
2.2 Many effect predictors (variables associated with responsiveness irrespective of treatment or non-treatment) and many effect modifiers (variables associated with differences in responsiveness to treatment) have been reported, such as those for treatment of depression. Similar effect predictors can be assumed for improvement of QOL, as listed below. Variables examined in this study will be based on those identified in original studies. However, if there are multiple variables that measure similar concepts, the study team will decide which variables to include in the models.

Others are in the appendix
Software Used:
I am not analyzing participant-level data / plan to use another secure data sharing platform
Project Timeline:

All candidate dates for the project are only estimation because it depens on the contrubution of the YODA project.
Project start date: End of May, 2022
Analysis completion date: End of the year 2022
Date manuscript drafted: End of March, 2023
First submitted for publication: End of the year 2023
Date results reported back to the YODA Project: End of the yaer 2023

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

Dissemination Plan:

All of the research findings report to the sponsor, Japanese Agency for Medical Research and Development, first. In order to disseminate the findings to contribute to furthering scientific knowledge, the results will be published in the peer-reviewed journal like Neuropsychopharmacology Reports and to the conference like the annual meeting of the Japanese Society of Neuropsychopharmaology.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/yoda_project_coi_form_for_data_requestors_2019.docx
https://yoda.yale.edu/sites/default/files/yoda_project_coi_form_for_data_requestors_2019_yoshie_omachi.pdf
https://yoda.yale.edu/sites/default/files/reserach_proposal_for_yoda_0.docx