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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: The Lundbeck Foundation
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/coi_soren_d_ostergaard_signed.pdf
https://yoda.yale.edu/system/files/coi_maria_speed.pdf
https://yoda.yale.edu/system/files/coi_anders_carlsen_2.pdf
https://yoda.yale.edu/system/files/coi_fredrik_hieronymus_2.pdf

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. NCT01009047 - R076477PSZ3003 - A Randomized, Multicenter, Double-Blind, Active-Controlled, Flexible-Dose, Parallel-Group Study of the Efficacy and Safety of Prolonged Release Paliperidone for the Treatment of Symptoms of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age

2. NCT00518323 - R076477PSZ3001 - A Randomized, Multicenter, Double-Blind, Weight-Based, Fixed-Dose, Parallel-Group, Placebo-Controlled Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age

3. NCT00334126 - R076477SCH3015 - A Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Paliperidone ER Compared to Quetiapine in Subjects With an Acute Exacerbation of Schizophrenia

4. NCT00589914 - R092670PSY3006 - A Randomized, Double-Blind, Parallel-Group, Comparative Study of Flexible Doses of Paliperidone Palmitate and Flexible Doses of Risperidone Long-Acting Intramuscular Injection in Subjects With Schizophrenia

5. NCT00590577 - R092670PSY3007 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia

6. NCT00210717 - R092670PSY3002 - A Randomized, Double-Blind, Parallel Group, Comparative Study of Flexibly Dosed Paliperidone Palmitate (25, 50, 75, or 100 mg eq.) Administered Every 4 Weeks and Flexibly Dosed RISPERDAL CONSTA (25, 37.5, or 50 mg) Administered Every 2 Weeks in Subjects With Schizophrenia

7. NCT00210548 - R092670PSY3003 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (50 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia

8. NCT00101634 - R092670PSY3004 - A Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq, 50 mg eq, and 100 mg eq) of Paliperidone Palmitate in Patients With Schizophrenia

9. NCT00034749 - RIS-USA-231 - The Efficacy and Safety of Risperidone in Adolescents With Schizophrenia: a Comparison of Two Dose Ranges of Risperidone

10. NCT00397033 - R076477SCA3001 - A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Two Dosages of Paliperidone ER in the Treatment of Patients With Schizoaffective Disorder

11. NCT00412373 - R076477SCA3002 - A Randomized, Double-blind, Placebo-controlled, Parallel- Group Study to Evaluate the Efficacy and Safety of Flexible-dose Paliperidone ER in the Treatment of Patients With Schizoaffective Disorder

12. NCT00249132 - RIS-INT-3 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients

13. NCT00077714 - R076477-SCH-304 - A Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 2 Fixed Dosages of Paliperidone Extended Release Tablets and Olanzapine, With Open-label Extension, in the Treatment of Patients With Schizophrenia

14. NCT00083668 - R076477-SCH-305 - A Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Paliperidone Extended Release (ER) Tablets and Olanzapine, With Open-label Extension, in the Treatment of Patients With Schizophrenia

15. NCT00074477 - R092670-SCH-201 - A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of 50 and 100 Mg-eq of Paliperidone Palmitate in Patients With Schizophrenia

16. NCT00078039 - R076477-SCH-303 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-Release (ER) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia

17. NCT00085748 - R076477-SCH-302 - A Randomized, 6-Week Double-Blind, Placebo-Controlled Study With an Optional 24-Week Open-Label Extension to Evaluate the Safety and Tolerability of Flexible Doses of

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

Research Proposal

Project Title

Factors moderating estimates of antipsychotic efficacy in schizophrenia

Narrative Summary:

Treatments for schizophrenia are assessed using rating scales. By comparing ratings between patients given different treatments (for example an antipsychotic or placebo) it is possible to assess which treatment is more efficacious.
In this study we wish to evaluate the performance of abridged versions (BPRS-6 and PANSS-6) of common rating scales for schizophrenia (BPRS and PANSS). We also aim to investigate if patient-level factors (e.g., age, sex, baseline symptom profile) moderate antipsychotic efficacy. The goals are i) to improve the rating of schizophrenia, thus bettering future clinical trials in this condition, and ii) to facilitate personalized medicine in schizophrenia.

Scientific Abstract:

Background Brief unidimensional subscales for schizophrenia have demonstrated superior psychometric properties as compared to full rating scales. They are also faster to administer and therefore more feasible to implement in clinical practice. In the current study we will compare the performance of two of these subscales to that of their comprehensive counterparts, as well as investigate to what extent patient-level predictors moderate the response to antipsychotic treatment, using patient-level data.
Objective i) To assess the performance of brief unidimensional subscales, BPRS-6 and PANSS-6, as compared to the full BPRS and PANSS rating scales in treatment trials in schizophrenia and ii) to investigate to what extent patient-level predictors (e.g., age, sex, baseline symptom profile) moderate treatment efficacy as measured by brief unidimensional subscales, single items, and full scales.
Study Design Individual patient-level data meta-analysis of acute-phase treatment trials in schizophrenia.
Participants Patients with schizophrenia treated with an established antipsychotic or placebo in acute-phase treatment trials.
Main Outcome Measure(s) Between-treatment contrasts of endpoint scores, and categorical derivates thereof (e.g., response), on brief unidimensional subscales (BPRS-6 and PANSS-6), single items and comprehensive rating scales (BPRS and PANSS).
Statistical Analysis Continuous outcome measures will be analyzed using Mixed Models for Repeated Measurements (MMRM) methodology, categorical outcome measures will be analyzed using generalized linear mixed models.

Brief Project Background and Statement of Project Significance:

Schizophrenia is a severe mental disorder characterized by abnormalities in thinking, perception, emotions and social function (1, 2). These characteristics have a profound negative impact on those living with schizophrenia (3, 4), as underlined by the fact that life expectancy of individuals with schizophrenia is approximately 20 years shorter than that of the background population (5).

While pharmacological treatments for schizophrenia have existed for more than 60 years, prescription decisions largely follow a "trial and error"-methodology (6, 7). It thus often takes several failed trials before effective antipsychotic treatment is initiated. Considering the vast humanitarian and societal impact of schizophrenia (8), and that duration of untreated psychosis predicts poor long-term outcomes (9), this gap in knowledge is highly unsatisfactory.

One reason that may have contributed to the difficulty in implementing personalized medicine for schizophrenia is the multidimensional rating scales used to evaluate disease severity. The traditional take has been that a good rating scale should offer exhaustive syndromal coverage. This position, while reasonable, is not without drawbacks since many psychiatric symptoms (e.g., insomnia or hypersomnia, somatic and psychic anxiety, concentration difficulties, loss of energy, gastrointestinal symptoms or weight changes) are not illness-specific, and can also be side effects of treatment. Similarly, the clinical impact of different symptoms, measured by the patient as functional impairment, varies greatly even though the symptoms may contribute the same amount of points to the rating scale sum-score (10).

In schizophrenia, the rating scale most widely used as outcome measure in clinical studies is the Positive and Negative Syndrome Scale (PANSS) (11). It has been demonstrated, across several patient populations (acute-, chronic- and treatment-resistant schizophrenia), that the full 30-item PANSS is highly multidimensional (12-14). However, a unidimensional 6-item subscale of PANSS (PANSS-6), which covers the following core positive and negative symptoms of schizophrenia: delusions, conceptual disorganisation, hallucinations, blunted affect, passive/apathetic social withdrawal and lack of spontaneity & flow of conversation, has demonstrated solid psychometric properties (12-14), including an increased sensitivity to the beneficial effects of some antipsychotics compared to the full PANSS (12). Similar findings have been reported for a shortened version (BPRS-6) of the Brief Psychiatric Rating Scale (BPRS), which is also commonly used in schizophrenia trials (15).
We aim to evaluate the psychometric performance of the BPRS-6 and the PANSS-6 as compared to the full BPRS and PANSS, respectively. If this evaluation supports the shorter scales as being psychometrically superior, then we will assess the impact of individual level predictors (e.g., age, sex, BMI, baseline symptom severity/profile) of interest. We hope that by using unidimensional subscales – which should be more consistent across different patient populations – we will have better power to identify clinically relevant effect modifiers.

Specific Aims of the Project:

The project has two overarching aims:
- To compare the psychometric performance of brief unidimensional subscales (PANSS-6 and BPRS-6) derived from commonly used schizophrenia rating scales (PANSS and BPRS). This will be done i) through Rasch analysis (item response theory analysis) investigating the scalability and transferability of the subscales and their comprehensive counterparts and ii) through contrasting drug-placebo separation between the unidimensional subscales and their multidimensional counterparts.
- To investigate the importance of putative patient-level effect modifiers (e.g., BMI, age, sex, dose, baseline symptom profile/severity, adverse event proneness) with regards to efficacy as measured by brief unidimensional subscales. To ensure that our results are comparable to previous investigations we well repeat all analyses using the full rating scales as effect parameters.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
Confirm or validate previously conducted research on treatment effectiveness
Participant-level data meta-analysis
Participant-level data meta-analysis using only data from YODA Project
Research on clinical trial methods
Research on clinical prediction or risk prediction

Research Methods

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

The data used in this study will come from the clinical trial programs of risperidone and paliperidone, with data access being provided by YODA. We will include all double-blind, acute-phase, placebo- and/or actively controlled trials of these compounds in schizophrenia or schizoaffective disorder, which utilized either PANSS, or BPRS, or both. Studies will be included regardless of treatment duration or participant age. Comparison arms against other established antipsychotics (e.g., haloperidol. olanzapine) will be included whereas any comparator arms against non-antipsychotic drugs will be excluded.

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

For the first part of the project, i.e., comparing the performance between brief unidimensional subscales and their comprehensive counterparts, the primary outcome measures will be those of a standard Rasch analysis (e.g., Andersen´s likelihood ratio test, Wald tests, tests of differential item functioning). We will also assess differences in responsiveness to change by contrasting endpoint effect sizes (standardized mean differences, SMDs, for continuous outcome parameters; odds ratios, ORs, for categorical outcome parameters e.g., response or remission) between rating scales, both for drug-placebo comparisons and for drug-drug comparisons.
For the second part of the project, i.e., assessing individual-level predictors, the main outcome measures will be the parameter estimates and levels of significance for the predictors (e.g., BMI, age, sex, baseline severity) when added to simplified models that do not control for these factors, as well as the differences in endpoint effect sizes between models that do and do not control for the respective factors.

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

The main predictor variables are: treatment, BMI, age, sex, baseline symptom severity (assessed either by BPRS or PANSS, or by their brief unidimensional counterparts), baseline symptom profile (assessed by individual BPRS and PANSS symptoms), early symptomatic improvement, and the presence of adverse events of interest. Predictor variables will primarily be included as continuous covariates, with potential interactions with treatment and/or trial, being checked in all analyses. Since specific levels for certain predictors may only be covered in certain studies (e.g., adolescents not being represented in studies focused on adults and vice versa), some comparisons will necessarily be indirect. In such cases we will conduct also stratified analyses for each population.

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

Depending on data availability/feasibility we may contrast outcome as measured by PANSS-6, PANSS, BPRS-6, and BPRS to outcome as measured by CGI or an established quality of life scale (e.g., QOLS, SQLS).

Statistical Analysis Plan:

The scalability and transferability of the BPRS-6, BPRS, PANSS-6 and PANSS will be investigated using Rasch analysis (e.g., as implemented in the eRm, ltm, and difR packages in R). We will use conventional tests of differential item functioning, scalability and transferability, as well as graphical checks of model fitness to determine the performance of the different rating instruments. Sensitivity analyses – in addition to the tests of differential item functioning – in relevant subpopulations (e.g., studies conducted in different regions, studies on adolescents) may be included if deemed appropriate.
Continuous outcome measures will be analyzed using Mixed Models for Repeated Measurement (MMRM) methodology. The dependent variables will be all post-baseline evaluations up until the endpoint evaluation, or up until the last common evaluation point included in the majority of eligible studies (for maximum coverage). The models will include fixed factors for treatment, trial, time (usually in weeks), and the interaction between treatment and time. The decision to treat trial as a fixed factor is motivated by feasibility and based on previous experiences with using MMRM models in trials on major depression in which models specifying a random intercept and/or slope for trial tend to have convergence issues (16). Baseline severity on the corresponding effect measure will be included as a covariate. The within-subjects correlations over time will be modelled using an unstructured (co)variance matrix. If this fails to converge an autoregressive (co)variance matrix with heterogeneous variance will be tried, and if this fails to converge an autoregressive (co)variance matrix with heterogeneous variance will be fitted. Should models using all three different (co)variance matrices fail to converge we will explore other solutions,

e.g., other (co)variance structures, and/or excluding certain studies and/or some time-points from the primary analyses. Denominator degrees of freedom will be estimated using the Kenward-Roger approximation. Effects on continuous outcome measures will be reported as standardized mean differences to maximize comparability between different rating instruments.

Categorical outcome measures will be analyzed in an analogous fashion using Generalized Linear Mixed Models and effects on categorical outcome measures (e.g., response, remission) will be reported as odds ratios. Covariates and predictor variables of interest (see above) will primarily be included as continuous covariates while assessing potential interactions with treatment and/or trial. These analyses, however, will necessitate somewhat of a case-by-case methodology based on data availability/overlap between studies. We thus foresee that we may need to conduct also stratified analyses, or analyses of derivate measures (e.g., categorical derivatives, factor scores), as sensitivity analyses.

Considering the available sample size we judge that we will have adequate power to detect any clinically relevant effect modifiers for risperidone and paliperidone. For reference drugs with sparse data, however, power may be inadequate. This will be dealt with on a case-by-case basis and communicated in the resulting publications.

The issue of missing data will be partially mitigated by the use of MMRM and generalized linear mixed models. Sensitivity analyses will be done on the intention-to-treat population using LOCF methodology in order to assess the impact of this methodological decision. In cases where an outcome of interest or a potential effect modifier can be time-dependent (e.g., early side effects, early rating scale-assessed improvement or decline) we will conduct sensitivity analyses using different capture windows.

Software Used:

RStudio

Project Timeline:

We anticipate that the project can start as soon as we get data access approved by YODA. After that we believe that we will need approximately 3-4 months of preparatory work to familiarize ourselves with the data sets, assess the feasibility of the various analyses, and prepare the final analysis set(s). We believe that the analyses for the first part of the project will take roughly one month, whereas those for the second part are estimated to take roughly two months. During this process we will continuously iterate a draft of the corresponding article. We expect that finalizing each manuscript will take roughly one month after all analysis work is completed. We plan to publish at least one paper per objective, and thus expect the first manuscript to be ready for publication approximately six months after gaining data access, and the second manuscript approximately nine months after obtaining data access. We will report our results to YODA immediately prior to submitting for publication/presentation.

Dissemination Plan:

Publications stemming from the first part of the project are – due to the technical nature – likely to be primarily of interest for psychiatrists and researchers in psychiatry. As such, we will attempt to publish manuscripts stemming from this part firstly in high-impact specialist journals (e.g., American Journal of Psychiatry, Lancet Psychiatry, JAMA Psych, Molecular Psychiatry), and secondarily in lower ranked specialist journals.

Publications stemming from work related to the second objective (predictors of response and comparative efficacy of different antipsychotics) may be of importance for the general medical community. If any such findings do emerge we will pursue publication in a high-impact general medicine journal (e.g., NEJM, JAMA, The Lancet, BMJ, PLoS Med). If this is not feasible then we will follow the same publication plan as above.

We will further communicate our findings in symposia and poster form (if accepted) at relevant international conferences (2-3 times yearly), as well as through lectures and public events organized at our local universities (Aarhus university and the University of Gothenburg).

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