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Developing a Risk Score to Guide Individualized Treatment Selection in Attention Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: To develop a risk score for treatment failure that could potentially be used to individualize treatment selection between lisdexamfetamine dimesylate (LDX) and osmotic-release oral system methylphenidate (OROS-MPH) in children and adolescents with attention deficit/hyperactivity disorder (ADHD). **Methods:** The study used data from patients with ADHD receiving LDX (N = 104) or OROS-MPH (N = 107) in a phase III randomized clinical trial. A prediction model was developed to estimate risk scores for failing OROS-MPH, where *treatment failure* was defined as less than 25% improvement in the ADHD Rating Scale IV total score from baseline. Patients were ranked by their predicted risks of OROS-MPH failure to define high-risk subpopulations. Outcomes of LDX and OROS-MPH were compared within subpopulations. **Results:** The prediction model for OROS-MPH failure selected seven predictors (age, disease duration, and five ADHD Rating Scale IV item scores) and had an in-sample *C* statistic of 0.860. Among all patients, LDX had a 17% (95% confidence interval 7.1%–27.8%) lower treatment failure rate than that of OROS-MPH; differences in failure rates ranged from 17% to 43% across subpopulations, increasingly enriched for high-risk patients. Similar heterogeneity across subgroups was observed for other efficacy measures. **Conclusions:** In the overall trial population, LDX was associated with a lower rate of treatment failure compared with OROS-MPH in patients with ADHD. A more pronounced benefit of LDX over OROS-MPH was observed among subpopulations with a higher predicted risk of failing OROS-MPH. The present study showed the feasibility of individualizing treatment selection. Future research is needed to prospectively verify these results.

Keywords: attention deficit/hyperactivity disorder, lisdexamphetamine dimesylate, personalized treatment selection, treatment individualization.

Introduction

The importance of treatment individualization in mental and neurologic diseases has been widely recognized [1–4]. The evidence available to inform individualized use of medication for attention deficit/hyperactivity disorder (ADHD), however, has remained limited. Current treatment assignment is primarily based on overall average treatment effects demonstrated in clinical trials, experience of physicians or patients, safety concerns, cost consideration, and patient/caregiver preferences [5–8]. To further optimize patient care in ADHD, evidence that can help guide the selection of therapies in ADHD in clinical practice could prove useful.

ADHD is a common neuropsychiatric disorder affecting 5.3% of children and adolescents worldwide [9]. Lisdexamfetamine dimesylate (LDX) and osmotic-release oral system methylphenidate (OROS-MPH) are two commonly used long-acting drugs for ADHD from two classes of first-line medication, amphetamine and methylphenidate, respectively [10,11]. No published clinical trial has been specifically and prospectively designed to compare the efficacy of OROS-MPH and LDX. A phase III clinical trial SPD489-325 (NCT00763971) aimed to evaluate the efficacy and safety of LDX in comparison with placebo and included an OROS-MPH arm; however, the comparison of LDX and OROS-MPH was not prespecified in the trial protocol. A post hoc analysis showed that LDX, on average, was associated with superior efficacy compared with OROS-MPH in terms of improvements in ADHD Rating Scale IV (ADHD-RS-IV) total score and the proportion of patients showing clinical improvements, defined by changes in ADHD-RS-IV total score from baseline exceeding a certain threshold and/or Clinical Global Impressions-Global Improvement (CGI-I) score [12,13]. The post hoc analysis, however, did not evaluate whether the benefit of LDX versus OROS-MPH was consistent or heterogeneous across different patient subgroups. It is our hypothesis that the benefit of LDX versus OROS-MPH could be heterogeneous across patient subgroups.

Heterogeneity in patients' responses to different therapies calls for individualized treatment selection. Pharmacogenetics, as

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the most commonly discussed approach to individualize treatment selection, holds great promise with the advancement of biotechnology. In the near term, however, the clinical application of pharmacogenetics in ADHD could be limited because consistent evidence linking genotypes to phenotypic responses to ADHD treatments is still lacking [14–17]. Well-validated models predicting treatment efficacy using readily available patient and disease characteristics can potentially provide a timely and practical approach to individualize treatment selection in future clinical practice.

The present study developed a predictive model for the risk of failing OROS-MPH. Risk scores derived from this model were used to classify patients into subgroups. Among these subgroups, responses to LDX and OROS-MPH were compared to assess whether the difference of LDX and OROS-MPH varied across patient subgroups. The risk scores could potentially be used to individualize treatment selection between LDX and OROS-MPH in children and adolescents with ADHD [18,19].

Methods

Study Population

The present study was a post hoc analysis of the SPD489-325 trial (NCT00763971), which was a phase III, randomized, double-blind, multicenter, placebo- and active-controlled study conducted across Europe. A detailed description of the trial can be found elsewhere [12]. In brief, the trial included children and adolescents (aged 6–17 years) with an ADHD diagnosis, based on the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) criteria of ADHD. Eligible patients had ADHD of at least moderate severity (baseline ADHD-RS-IV total score of $\geq$28). A total of 336 subjects were randomized at the 1:1:1 ratio to be subsequently treated for 7 weeks with LDX, OROS-MPH, or placebo. Patients randomized to LDX or OROS-MPH who received at least one dose of the investigational product were included in the current analyses.

Study Measures

Data on demographic characteristics, weight, height, body mass index, disease characteristics, and previous ADHD treatment were collected at baseline. For the current analyses, the outcome variables were evaluated at week 7 and included 1) *Treatment failure*: defined as less than 25% improvement in ADHD-RS-IV total score from baseline; 2) *Treatment response*: defined as 25% or more improvement in ADHD-RS-IV total score from baseline, that is, opposite of treatment failure (alternative definitions using $\geq$30% and $\geq$50% improvement cutoffs were considered in sensitivity analyses); 3) Change in ADHD-RS-IV score (total score, hyperactivity/impulsivity and inattentiveness subscale scores); 4) CGI-I response (achieving CGI-I of either "very much improved" or "much improved"); 5) Composite response ($\geq$30% improvement in ADHD-RS-IV total score from baseline and achieving CGI-I response); 6) Change in health-related quality of life measured by Child Health and Illness Profile-Child Edition: Parent Report Form (CHIP-CE: PRF), (global *T* scores and domain scores); and 7) Change in functional impairment measured with Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) (global scores and domain scores). Treatment failure is defined as less than 25% improvement in ADHD-RS-IV total score from baseline in the present study because the 25% cutoff is widely used in the ADHD literature, and at least 25% improvement is considered a clinically detectable response to treatment in patients with ADHD [20–27].

Descriptions of Baseline Characteristics and Efficacy of LDX and OROS-MPH in the Overall Population

Patients' baseline characteristics and efficacy outcomes at week 7 were summarized for both LDX and OROS-MPH arms. Means and SDs were calculated for continuous variables, and counts and proportions were calculated for categorical variables. For efficacy outcomes at week 7, differences in means of continuous variables between the two treatment arms were compared using two-sample *t* tests, and differences in categorical variables were compared using chi-square tests (or Fisher exact test if $\geq$25% of the cells had expected counts $<$5). The last observation carried forward method was used to impute the efficacy outcomes at week 7 by carrying forward the last available postbaseline measure to week 7 when there were missing values.

Development of a Prediction Model for Risk of Failing OROS-MPH

A logistic regression model was fit using the data of all OROS-MPH patients in the study sample to predict failure to OROS-MPH. A least absolute shrinkage and selection operator (LASSO) approach was applied to select an optimal set of covariates from a list of candidate covariates [28]. Instead of selecting one covariate at a time or predefining a list of covariates, the LASSO method allowed simultaneous selection of a set of variables predictive of OROS-MPH treatment failure. The list of candidate covariates considered included age, sex, race, body mass index, ADHD subtype, disease duration, comorbidities, previous ADHD pharmacologic and behavioral treatment, and disease severity measured by ADHD-RS-IV item scores. The *C* statistic and the Hosmer-Lemeshow statistic were computed to evaluate the fit of the model.

Attempt was also made to develop a prediction model for the risk of failing LDX; however, because of the limited heterogeneity in the treatment failure rate to LDX (i.e., the low failure rate of 9.2% among LDX-treated patients), an intercept-only model was obtained, which was not suitable for individualizing treatment selection.

Comparison of Efficacy Outcomes across Patient Subgroups

Differences in efficacy outcomes between LDX and OROS-MPH across patient subgroups were depicted using treatment difference curves. On these curves, differences in the observed rates of treatment failure to LDX and OROS-MPH were plotted (Y-axis) by subpopulations increasingly enriched for patients with high risk to fail OROS-MPH (X-axis). Randomized Monte-Carlo cross-validation was used to construct such curves. Specifically, patients in the study sample were randomly split to training (60% of OROS-MPH–treated patients) and validation (40% of OROS-MPH–treated patients and all LDX-treated patients) samples. A logistic regression model, using the covariates selected by the LASSO approach, was fit to the training sample; the fitted model was applied to the validation sample to obtain patients' risk scores of failing OROS-MPH. Patients were ranked by their risk scores and were sequentially grouped together by 10% increments, starting from the top 30% of patients with the highest risk scores (this cutoff was selected because of the sample size: there are $<$10 OROS-MPH patients if the 20% threshold is used), until all patients (100%) were included. The subpopulation size and the respective risk score thresholds to form the subpopulation were both provided on the X-axis. Within each of these cumulative subgroups, the actual observed rates of treatment failure to LDX and OROS-MPH and the difference in these observed rates were calculated, and the average rates across the 2000 iterations in the randomized Monte-Carlo cross-validation were used for plotting. Bootstrapping was used to create the 95% confidence interval (CI) for the