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Predictors of treatment outcome in adults with ADHD treated with OROS® methylphenidate

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ABSTRACT

Background: We conducted a *post-hoc* analysis of the Long-Acting MethylpheniDate in Adult attention-deficit hyperactivity disorder (LAMDA) study to investigate predictors of response in adults with ADHD randomly assigned to Osmotic Release Oral System (OROS)®-methylphenidate hydrochloride (MPH) 18, 36 or 72 mg or placebo.

Methods: LAMDA comprised a 5-week, double-blind (DB) period, followed by a 7-week, open-label (OL) period. A *post-hoc* analysis of covariance and a logistic regression analysis were undertaken to detect whether specific baseline parameters or overall treatment compliance during the double-blind phase contributed to response. The initial model included all covariates as independent variables; a backward stepwise selection method was used, with stay criteria of $p<0.10$. Six outcomes were considered: change from baseline CAARS: O-SV (physician-rated) and CAARS:S-S (self-report) scores at DB and OL end points, and response rate (≥30% decrease in CAARS:O-SV score from baseline) and normalization of CAARS:O-SV score at DB end point.

Results: Taking into account a significant effect of OROS®-MPH treatment *versus* placebo in the original analysis ($p\leq0.015$), across the outcomes considered in this *post-hoc* analysis, higher baseline CAARS scores were most strongly predictive of superior outcomes. Male gender and lower academic achievement were also predictive for improved results with certain outcomes.

Conclusions: Several baseline factors may help to predict better treatment outcomes in adults receiving OROS®-MPH; however, further research is required to confirm these findings and examine their neurobiological underpinnings.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a heterogeneous and highly heritable disorder, manifesting itself in symptoms of inattention and/or hyperactivity/impulsivity that arise during childhood, frequently persistent throughout development into adulthood, and result in impairment in multiple domains of functioning (Barkley et al. 2002; Faraone et al. 2005; Biederman et al. 2006a; Faraone et al. 2006; Fried et al. 2006; Li et al. 2006). Pharmacotherapy is central in the management of ADHD, with methylphenidate hydrochloride (MPH) a cornerstone of treatment. MPH is recommended as first-line therapy in the treatment of children, adolescents and adults with ADHD based on a recent evaluation made by the British National Institute for Health and Clinical Excellence (NICE) (National Institute for Health and Clinical Excellence 2008). Notably, results from the

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ANCOVA, analysis of covariance; CAADID, Conners' Adult ADHD Diagnostic Interview for DSM-IV; CAARS:O-SV, Conners' Adult ADHD Rating Scale (physician rated); CAARS:O-S-S, Conners' Adult ADHD Rating Scale (self-reported, short version); CI, confidence interval; DB, double-blind; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth edition; LAMDA, Long-Acting MethylpheniDate in Adult attention-deficit hyperactivity disorder; LOCF, last observation carried forward; MPH, methylphenidate hydrochloride; NICE, National Institute for Health and Clinical Excellence; OL, open-label; OR, odds ratio; OROS, Osmotic Release Oral System; SE, standard error.

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LAMDA study (Long-Acting MethylpheniDate in Adult attention-deficit hyperactivity disorder) [protocol 42603ATT3002], which was a large, 5-week, double-blind, placebo-controlled study (Medori et al. 2008), with a 7-week, open-label extension phase (Buitelaar et al. 2009), demonstrated the efficacy, safety and tolerability of OROS®-MPH in adults with ADHD. In this study, significant improvements in the scores in both the physician-rated version of Conners' Adult ADHD Rating Scale (CAARS:O-SV) and the self-reported, short version (CAARS:S-S) from baseline to double-blind end point were observed for all OROS®-MPH dosages (18 mg, 36 mg or 72 mg) compared with placebo ($p \leq 0.015$ for all comparisons *versus* placebo); as expected, results for physician-rated and self-rated CAARS scores showed similar trends. Likewise, the proportion of responders (≥30% reduction in CAARS:O-SV total score) was significantly higher in the OROS®-MPH groups compared with placebo (Medori et al. 2008). In addition, the safety and tolerability profile in adults was comparable to that observed in children and adolescents.

Although generally considered effective, reported response rates to MPH in adults with ADHD are quite variable (Kooij et al. 2004; Rösler et al. 2004; Kessler et al. 2006; Rösler et al. 2009). The reasons behind variability in response to therapy in ADHD are not fully understood. Associated co-morbidities have been shown to alter response to ADHD therapy (Ghuman et al. 2007; Newcorn 2009), while other factors, such as female gender, higher IQ, considerable inattentiveness, younger age, lower disease burden and compliance with stimulant medication may also account for variability of treatment response in children and adolescents with ADHD (August et al. 1983, Buitelaar et al. 1995; Hechtman 1999; van der Oord et al. 2008, MTA Cooperative Group, 1999). It has, however, been consistently observed that higher dosing of stimulants result in a higher percentage of responders (Spencer et al. 1995; Faraone et al. 2004; Biederman et al. 2006b; Medori et al. 2008).

Whilst results from the LAMDA study demonstrate that adults with ADHD generally show good symptomatic improvement with MPH therapy, predicting response in individual patients above and beyond medication status remains somewhat elusive. Therefore, to further knowledge in this area, we report the results of a *post-hoc* analysis of the aforementioned LAMDA study, which was undertaken to investigate the influence of baseline characteristics and treatment variables on clinical outcomes in adults with ADHD.

2. Methods

2.1. Study design and patients

This study has been previously described in detail. In brief, this was a 5-week, double-blind, randomized, placebo-controlled, parallel-group, 4-arm, fixed-dose trial (Medori et al. 2008), followed by a 7-week, open-label phase (Buitelaar et al. 2009) in adult men and women (aged 18–65 years) with a diagnosis of ADHD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV), criteria. Presence and chronicity of childhood symptoms were confirmed by the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Conners C et al. 1999). Other requirements for inclusion were a CAARS:O-SV score of ≥24 points at screening.

Following screening and a washout period of up to 4 weeks during which current therapy was tapered to discontinuation, eligible patients were randomly assigned into one of four treatment groups to receive once-daily oral dosages of 18 mg, 36 mg or 72 mg OROS®-MPH or placebo. Patients in the 72 mg OROS®-MPH group were titrated from a starting dose of 36 mg/day for 4 days to 54 mg/day for 3 days, after which 72 mg/day was administered for 4 weeks.

Following the double-blind treatment phase, eligible patients entered the 7-week, flexible-dose, open-label extension phase with OROS®-MPH, during which all patients were initiated on OROS®-MPH at 36 mg/day, with the exception of the German patients who started with 18 mg/day. Patients were flexibly dosed, based on investigator assessment, between 18 and 90 mg/day total daily dose. Participants gave written informed consent. The study was reviewed and approved by the institutional review board of each participating centre. All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation and the Declaration of Helsinki, 1983 (see for the latest version www.wma.net).

2.2. Statistical analyses

2.2.1. Predictive value of baseline characteristics

A *post-hoc* analysis of covariance (ANCOVA) and a logistic regression analysis were undertaken to detect which baseline parameters contributed to the effect of OROS®-MPH or, in other words, which baseline parameters could be considered as predictors of treatment response. Six different outcome measures were considered: change from baseline in CAARS:O-SV score at the end of the 5-week, double-blind treatment period (1), or at the end of the subsequent 7-week, open-label extension phase (2); change from baseline in CAARS:S-S score: short version score at the end of the 5-week, double-blind treatment period (3), or at the end of the subsequent 7-week, open-label extension phase (4); response rate at the end of the 5-week, double-blind treatment period, where response was defined as a 30% or greater decrease in CAARS:O-SV score from baseline (5); and rate of normalization of CAARS:O-SV score at the end of the 5-week, double-blind treatment period, where normalization was defined as a return of CAARS:O-SV score to within the normal range according to the specifications provided in the CAARS manual (6). A last observation carried forward (LOCF) imputation method was utilized for missing values.

The CAARS:O-SV comprises 18 investigator-rated items corresponding to the 18 DSM-IV ADHD symptoms and provides a total score referred to as the CAARS total ADHD symptom score and two subscales. As patient ratings are a valuable source of additional data, the CAARS:S-S was also utilized. This is a 26-item, self-reported, four-point rating scale that measures symptoms based on the DSM-IV criteria for ADHD, providing a total score, ADHD index and four subscales. Change in CAARS:O-SV and CAARS:S-S scores (absolute measure) were assessed as continuous efficacy parameters using ANCOVA models; response (based on relative change) and normalization rates were assessed as binary efficacy parameters using logistic regression.

The following nine parameters, which were assessed at screening or baseline, were used in the analysis: (1) age (years), (2) gender (male/female), (3) history of mood or anxiety disorders (yes/no), (4) history of drug or alcohol abuse (yes/no), (5) country (Czech Republic, Denmark, Finland, France, Germany, Greece, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom), (6) highest education level (on a 4-point scale: primary school, secondary school, high school or university); (7) employment status at baseline (yes/no); (8) baseline score of CAARS:O-SV or CAARS:S-S, respectively; and (9) randomization treatment group (placebo, OROS®-MPH 18 mg, OROS®-MPH 36 mg and OROS®-MPH 72 mg). Overall treatment compliance during the double-blind phase was also included in the analysis as the only non-baseline variable; compliance was calculated as the number of tablets actually taken during the double-blind phase, divided by the scheduled number of tablets. Baseline age and CAARS:O-SV and CAARS:S-S scores, and overall treatment compliance were included as continuous variables, with the other parameters analysed as categorical variables. The relation between the predictors and each of the outcomes was evaluated using correlation coefficients or visual inspection of cross-tabulations as applicable.

All analyses used a stepwise approach. The initial model included all parameters as independent variables. The least significant covariate was then eliminated and the analysis repeated with one