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Predicting efficacy of viloxazine extended-release treatment in adults with ADHD using an early change in ADHD symptoms: Machine learning *Post Hoc* analysis of a phase 3 clinical trial

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ABSTRACT

Early response to viloxazine extended-release (viloxazine ER, Qelbree®) treatment predicted efficacy outcome in pediatric subjects with attention-deficit/hyperactivity disorder (ADHD). This study sought to determine whether the machine learning lasso model used in the pediatric study would predict response to viloxazine ER in an adult population based on early improvements in ADHD symptoms. We used data from a double-blind, placebo-controlled, flexible-dose (200–600 mg) study of viloxazine ER ($N = 354$; 18 to 60 years old). Area under the Receiver Operating Characteristic Curve (ROC AUC) statistics were computed using the lasso model from pediatric data to predict responder status in adults. Response was defined as ≥50% reduction from baseline in the Adult ADHD Investigator Symptoms Rating Scale (AISRS) Total score at Week 6. The adult study sample included 127 viloxazine ER-treated subjects with Week 6 data. Fifty-one subjects (40.2%) were categorized as responders. The ROC curves indicated that data collected up to Week 2 were sufficient to accurately predict treatment response at Week 6 with 68% positive predictive power, 80% sensitivity, and 74% specificity. This analysis demonstrated that the predictive model estimated from the child data generalizes to adults with ADHD, further supporting the consistency of viloxazine ER treatment across age groups.

1. Introduction

Viloxazine extended-release (viloxazine ER, viloxazine extended-release capsules; Qelbree®) is a medication approved by the US Food and Drug Administration for treating attention-deficit/hyperactivity disorder (ADHD) in children and adolescents (ages 6–17 years) (Nasser et al., 2021a, b; Nasser et al., 2020; Nasser et al., 2021c, d). A Phase 3 clinical trial recently demonstrated efficacy and safety in adults with ADHD (Nasser et al., 2021a). Being the first nonstimulant medication approved for ADHD in over a decade, if approved in adults, it will also become one of two nonstimulant treatment options available for adult ADHD (along with atomoxetine) (Cutler et al., 2020).

Psychostimulants are the first-line pharmacological therapy for ADHD, and nonstimulants are usually considered for those individuals for whom stimulants have been proven to be ineffective, intolerable, or contraindicated (Faraone et al., 2015; Wolraich et al., 2019). The main reasons for this approach are the higher effect size and rapid response to stimulant medications and the lack of predictors of treatment response (Cortese, 2020; Cortese et al., 2018). Although accurate predictors of treatment response have been difficult to establish, our recent *post hoc* analysis of data from child and adolescent clinical trials of viloxazine ER found that early response after two weeks of treatment with viloxazine ER can predict efficacy outcome at Week 6 with a level of accuracy sufficient for use in clinical practice (Faraone et al., 2021). Treatment response was defined as having a ≥50% reduction (improvement) from baseline in ADHD symptoms at Week 6 as measured with the ADHD Rating Scale, 5th Edition (ADHD-RS-5) Total score. The study used a machine learning analysis with 50-fold cross-validation and evaluated accuracy using a separate dataset that had not been used for the model estimation. Based on the best selected model, lasso regression, using the change in the ADHD-RS-5 Total score at Week 2, we could select 75% of patients who would respond by Week 6.

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A predictive modeling study of another nonstimulant medication for ADHD, atomoxetine, used a pooled sample from six pediatric clinical trials and defined responders as having a ≥40% decrease in the ADHD Rating Scale, 4th Edition (ADHD-RS-IV) Total score (Newcorn et al., 2009). The model required 4 weeks of treatment to make a prediction that achieved a level of accuracy similar to what was found for viloxazine ER at 2 weeks using a response definition of ≥50% decrease in the ADHD-RS-5 (Faraone et al., 2021). However, unlike the viloxazine study, the atomoxetine study did not use a separate dataset to reduce estimation bias of predictive accuracy. Several other studies previously attempted to predict the response to ADHD medications, including some machine learning applications. Despite these efforts, no clinically useful predictive model has been developed for adults (Hermens et al., 2005; Ishii-Takahashi et al., 2015; Kim et al., 2015; Ogrim et al., 2014; Ogrim and Kropotov, 2019; Wong et al., 2017).

The goal of the present work was to assess the accuracy of the predictive model we previously developed for children and adolescents (Faraone et al., 2021) when applied to a new dataset of adults with ADHD who were treated with viloxazine ER. The primary data from the clinical trial of adults with ADHD have been reported elsewhere (Nasser et al., 2021a). We hypothesized that the lasso model we had developed from the pediatric study data would predict response to treatment with viloxazine ER in adults and that the level of predictive accuracy would be similar to what we had observed for children and adolescents.

2. Methods

2.1. Data description

This *post hoc* analysis used data from a randomized, double-blind, placebo-controlled, flexible-dose study of viloxazine ER (NCT04016779) (Nasser et al., 2021a).

Adult subjects (18 to 65 years of age) were included in the study if they had a primary diagnosis of ADHD per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (within at least 6 months prior to screening) confirmed with Structured Clinical Interview for DSM-5 Clinical Trials version at screening, an Adult ADHD Investigator Symptoms Rating Scale (AISRS) Total score of ≥26, and a Clinical Global Impression-Severity scale score ≥4. Subjects were required to be medically healthy and have a body mass index (BMI) of ≥18.0 and ≤35.0 kg/m^2. Subjects were not eligible to participate if they had a history of intolerance or allergic reaction to viloxazine or its excipients, had a positive drug test at screening, had a current diagnosis or history of substance use disorder, or were chronic or habitual cannabis users. Subjects with a secondary diagnosis of major depressive disorder, generalized anxiety disorder, social anxiety disorder, phobia, or nicotine dependence were allowed if they were not receiving pharmacological treatment for the comorbidity/secondary diagnoses at the time of screening and the duration of study.

The study protocol was approved by WIRB-Copernicus Group and conducted in accordance with the Helsinki Declaration and the International Council for Harmonisation Good Clinical Practice Guidelines. Each subject provided written informed consent prior to screening.

Subjects were randomized to receive the study medication (viloxazine ER or a matching placebo) administered as oral capsules once daily in the morning with or without food. Subjects received 200 mg/day of study medication during Week 1, 400 mg/day during Week 2, and 200 to 600 mg/day during Weeks 3–6 (dose could be adjusted up/down in increments/decrements of 200 mg/day per week at the investigator's discretion based on the subject's clinical response and tolerability).

2.2. Data analysis

All viloxazine ER-treated subjects who had data at Week 6 were included in the analysis. Since the goal of this analysis was to predict the response to viloxazine ER, the data of placebo-treated subjects were not included.

As in the previously published pediatric analysis, a responder to viloxazine ER treatment was defined as a subject who had a ≥50% reduction (improvement) in their change from baseline (CFB) AISRS Total score at Week 6 (Faraone et al., 2021). The following variables were used to predict response at Week 6: AISRS Total score, age, body weight, and BMI at baseline; change from baseline in AISRS Total score at Week 1, cumulative change in AISRS Total score at Week 2, and cumulative change in AISRS Total score at Week 3; Clinical Global Impressions-Improvement (CGI-I) score at Week 1, 2, and 3; and target dose.

We used the lasso model hyperparameters estimated from the pediatric study (Faraone et al., 2021) to classify the adult subjects as responders or non-responders. Model accuracy was assessed by computing the Area under the Receiver Operating Characteristic Curve (ROC AUC) and 95% confidence interval (CI). The analysis was conducted using glmnet software package of The R Foundation for Statistical Computing (Version 4.0.0). This package fits a generalized linear model via penalized maximum likelihood.

3. Results

The demographic and baseline characteristics of the study population and the study results were previously reported (Nasser et al., 2021a). The intent-to-treat population consisted of 354 adult subjects (age: mean + standard deviation, range; 34.8 + 10.1, 18 to 60 years of age) treated with viloxazine ER (n = 175) or placebo (n = 179). The study sample included 127 viloxazine ER-treated subjects who had data at Week 6. There were 51 subjects in this sample (40.2%) who were categorized as a responder to viloxazine treatment.. Descriptive statistics for responders and non-responders for all continuous variables are summarized in Table 1. Twenty-seven (52.9%) responders were male and 24 (47.1%) were female. Among non-responders, 46 (60.5%) were male and 30 (39.5%) were female.

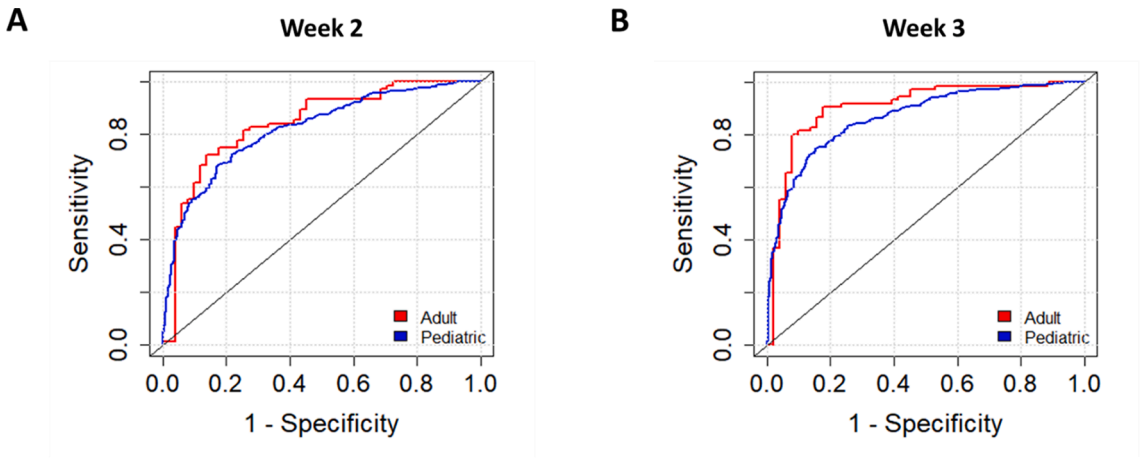
The ROC AUC statistics and 95% CIs were computed by applying the pediatric lasso model to predict responder/non-responder status in the adult data at Week 6. The ROC curves are provided in Fig. 1. The ROC AUC values increased with increasing numbers of weeks of data: 0.91 (95% CI: 0.85–0.97) when using data up to Week 3 compared with 0.84 (95% CI: 0.77–0.91) when using data up to Week 2 for the adult population. The 95% confidence intervals in Fig. 1 show that the magnitude of predictive accuracy was the same for the pediatric and adult data.

The precision-recall curves in Fig. 2 show two clinically useful statistics. The sensitivity gives the probability that the model will detect a true responder. The positive predictive power (PPP) gives the

Table 1
Descriptive statistics of variables by responder status

Variable	Responders (n = 51)		Non-responders (n = 76)	
	Mean	SD	Mean	SD
Dose (mg)	482.35	133.72	528.95	116.41
Age (years)	35.69	9.14	33.14	10.47
Body weight (kg)	83.00	18.74	79.86	15.98
BMI (kg/m^2)	28.20	4.75	26.92	4.68
CGI-I score at Week 1	2.88	0.84	3.61	0.63
CGI-I score at Week 2	2.45	0.76	3.46	0.77
CGI-I score at Week 3	1.92	0.77	3.17	0.79
AISRS Total score at baseline	39.33	6.09	38.16	6.84
CFB in AISRS Total score at Week 1	13.06	10.18	4.14	5.74
Cumulative change in AISRS Total score at Week 2	5.04	7.91	1.75	5.10
Cumulative change in AISRS Total score at Week 3	5.73	8.82	2.53	4.97

Abbreviations: AISRS, Adult ADHD Investigator Symptoms Rating Scale; BMI, body mass index; CFB, change from baseline; CGI, Clinical Global Impression-Improvement; n, number of subjects; SD, standard deviation



Population	ROC AUC	Lower 95% CI	Upper 95% CI
Adult	0.84	0.77	0.91
Pediatric	0.82	0.79	0.85

Population	ROC AUC	Lower 95% CI	Upper 95% CI
Adult	0.91	0.85	0.97
Pediatric	0.86	0.83	0.89

Fig. 1. ROC curves estimated in adult and pediatric populations using data up to Week 2 (A) and up to Week 3 (B)
Abbreviations: AUC, area under the curve; CI, confidence interval; ROC, Receiver Operating Characteristic.

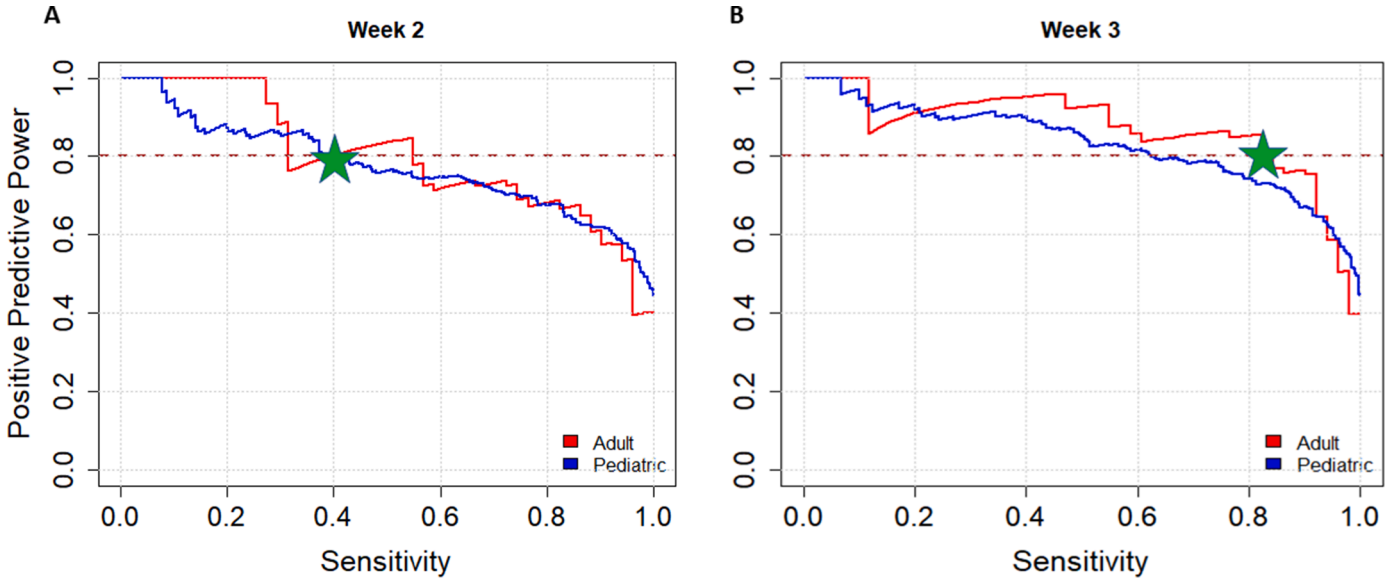


Fig. 2. Precision-recall curves estimated in adult and pediatric populations using data up to Week 2 (A) and up to Week 3 (B)
The horizontal dotted lines indicate Positive Predictive Power = 0.8.

probability that a patient selected by the model will respond at Week 6. The plots indicate that the data from either Week 2 or Week 3 could be used to make accurate predictions of the efficacy outcome at Week 6.

The plots indicate that the data from either Week 2 or Week 3 could be used to make accurate predictions of the efficacy outcome at Week 6. As the horizontal dotted line shows, using three weeks of data, the lasso model identified adult responders with a sensitivity of 82% and a PPP of 80% at Week 6 (see highlighted point on Fig. 2).

4. Discussion

In this analysis of data from the Phase 3 clinical trial of viloxazine ER in adults with ADHD, the predictive model developed from four Phase 3 pediatric clinical trials accurately predicted treatment response at a level that was consistent with what was obtained in the pediatric study (Faraone et al., 2021). As we had seen with the pediatric data, for the adult data, it is possible to make clinically meaningful predictions as early as 2 weeks after initiation of treatment based on improvement in symptoms. To the best of our knowledge, this is the first clinically useful predictive model developed for the psychopharmacotherapy of adults with ADHD.

The clinical utility of our results is best seen in the precision-recall curves (Fig. 2), which show two clinically relevant probabilities. The sensitivity (model's ability to select patients who will respond) is plotted on the horizontal axis. The PPP (probability that a patient predicted to be a responder will respond at Week 6) is plotted on the vertical axis. When we used data up to Week 2 (Fig. 2A), the precision-recall curves for the adult and pediatric populations were almost identical. When using data up to Week 3 (Fig. 2B), the precision-recall curves for adults and pediatric subjects were also similar, although the difference

between them was more pronounced at higher levels of sensitivity. This small difference between the plots and the "smoother" curve for pediatric subjects is likely due to the much larger sample size of the pediatric population.

Consider an example of 100 viloxazine ER-treated adult patients in clinical practice who would have the same response rate as in this study (40.2%). When we apply our predictive algorithm using the 80% sensitivity/68% PPP threshold for identifying responders, the lasso model at Week 2 would select 48 patients to continue and 52 to discontinue the treatment. Our model would predict 33 of the 48 patients to be future responders so they would receive at least six weeks of treatment. The results of this analysis are consistent with those previously reported in the pediatric population with viloxazine ER (Faraone et al., 2021).

Strengths of our study include 50-fold cross-validation, the evaluation of accuracy in a separate dataset, and the use of a high threshold to define treatment response (≥50% reduction in the CFB AISRS Total score at Week 6). At this threshold, 40.2% of subjects were identified as responders. This percentage is consistent with the pediatric data (44% responders) (Faraone et al., 2021). The limitations of this work include the relatively small sample size of the adult study compared with the pediatric study. The use of larger samples might increase predictive accuracy. In addition, these findings reflect the characteristics of the patient population enrolled in a controlled clinical trial, which may not be reflective of the real-world population of adults with ADHD. The predictive features in this study required the symptoms to be assessed with AISRS at weekly visits, which may not be feasible in some settings. Finally, because the response rate is incorporated into the computation of PPP and NPP, if the base response rate to viloxazine ER differs from the response rate observed in our work, the results will not be exact.

Despite these limitations, these data confirm that the method developed for predicting the efficacy response to viloxazine ER in children and adolescents (6 to 17 years of age) with ADHD can be applied to adults (18 to 65 years of age) with ADHD. Taken together, the data from this and the pediatric study (Faraone et al., 2021) show the consistency of the viloxazine ER effect on ADHD symptoms across different age groups and suggest that 2 weeks of treatment would be sufficient to predict the efficacy outcome of viloxazine ER treatment in children, adolescents, or adults.

Disclosures

JTH, SAC, GDB, ZM, WO, JR, and **AN** are employees of Supernus Pharmaceuticals, Inc.

In the past year, **SVF** received income, potential income, travel expenses, continuing education support and/or research support from Aardvark, Rhodes, OnDosis, Tris, Otsuka, Arbor, Ironshore, KemPharm/Corium, Akili, Supernus, Takeda, and Genomind. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received support from Shire, Ironshore, Enzymotec, Neurovance, Alcobra, Sunovion, Rhodes, KemPharm/Corium, CogCubed, Akili, Neurolifesciences, Takeda, Otsuka, McNeil, Janssen, Novartis, Pfizer, and Eli Lilly. He also receives royalties from books published by Guilford Press: *Straight Talk about Your Child's Mental Health*; Oxford University Press: *Schizophrenia: The Facts*; and Elsevier: *ADHD: Non-Pharmacologic Interventions*. He is Program Director of www.adhdinadults.com.

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