Overview of Viloxazine ER (Qelbree®) Preclinical, Post-Hoc, and Review Peer-Reviewed Publications

Preclinical	
Pharmacokinetics-ADME[1]	Viloxazine and major metabolite profile of absorption, distribution, metabolism and excretion. Viloxazine is not a significant inhibitor or inducer of CYPs or transporters, with the exception of CYP1A2.
Pharmacology[2]	In addition to NET inhibition, viloxazine is an antagonist of 5-HT7 and 5-HT2b, and a partial agonist at 5-HT2c. At doses tested, viloxazine increased neurotransmitter levels (NE, DA and 5-HT) 500-600% in the rat prefrontal cortex. Viloxazine does not have activity at SERT or DAT.
Pharmacology[3]	At doses relevant for the treatment of ADHD in children and adults, viloxazine significantly increased NE, DA, and 5-HT in the rat prefrontal cortex in a dose-dependent pattern.
Pharmacokinetic Modeling-Missing Dose[4]	After missing doses, viloxazine ER concentrations can return to steady-state levels after about 2 days of once-daily dosing.
Post-Hoc Analyses	
Early Response Prediction-Pediatrics[5]	Early partial response to viloxazine ER after 2 weeks of treatment in children and adolescents is a reliable predictor of efficacy after 6 weeks of treatment.
Early Response Prediction-Adults[6]	Similar to pediatric data, early partial response to viloxazine ER in adults after 2 weeks of treatment is a reliable predictor of efficacy after 6 weeks of treatment.
Correlation of Symptom Improvement and Clinician Assessment[7]	Translation of ADHD-RS-5 and WFIRS-P scores from phase 3 trials in children and adolescents treated with viloxazine ER to clinically meaningful CGI levels.
Likelihood to Help or Harm (LHH)[8]	Children and adolescents with ADHD taking viloxazine ER are likely to benefit from and unlikely to discontinue treatment due to favorable LHH, NNT, and NNH.
Functional Impairment[9]	In phase 3 trials of children and adolescents with ADHD, treatment with viloxazine ER significantly improved ADHD and functional impairment symptoms as early as 1-2 weeks.
Executive Function[10]	Viloxazine ER significantly reduced executive function deficits in children and adolescents with ADHD in phase 3 trials.
Learning and School Problems[11]	Viloxazine ER significantly improved learning and school problems in children and adolescents with ADHD in phase 3 trials.
Placebo Response in Pediatric Trials[12]	A band pass analysis of the four phase 3 pediatric studies found a higher placebo response in a phase 3, high-dose adolescent study (812P304), suggesting a failed trial.
Peer Relations and Social Activities[13]	Viloxazine ER significantly reduced impairments related to peer relations and social activities in 4 phase 3 studies in children and adolescents with ADHD.
Reviews	
Functional Improvement-Narrative Review[14]	Narrative review of evidence showing pharmacological treatment can be effective in minimizing the symptoms and functional consequences of ADHD.

Abbreviations: ER: Extended-release; **CYP:** CYP P450 enzymes; **5-HT**: serotonin; **NET**: norepinephrine reuptake transporter; **NE**: norepinephrine; **DA**: dopamine; **ADHD:** Attention-deficit/hyperactivity disorder; **ADHD-RS-5:** Attention-deficit/hyperactivity disorder rating scale-5; **WFIRS-P:** Weiss functional impairment rating scale – parent report; **CGI:** Clinical global impression scale; **LHH:** Likelihood to be helped or harmed; **NNT:** number needed to treat; **NNH:** number needed to harm

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