

Elexacaftor/Tezacaftor/Ivacaftor Therapy: Impact on The Mental Health of Children and Adolescents with Cystic Fibrosis

Alberto Vidal Grell^{1*} and Marcela Matamala Bastian²

¹Division of Pediatric Pulmonology, Department of Pediatrics, Clínica MEDS, Chile

²Division of Child and adolescent psychiatry, Clínica MEDS, Chile

Submission: August 17, 2026; **Published:** August 26, 2026

***Corresponding author:** Alberto Vidal Grell, MD, Avenida José Alcalde Délano 10581, Lo Barnechea, Santiago, Chile

Abstract

Triple therapy with transmembrane conductance regulator modulators has demonstrated notable improvements in pulmonary, pancreatic, and nutritional function in patients with cystic fibrosis. Concurrently, various adverse effects associated with this therapy have emerged, with symptoms affecting patients' mental health drawing particular attention. Current evidence is contradictory, making it impossible to establish a causal link between triple therapy and either favorable or unfavorable mental health outcomes in children and adolescents with cystic fibrosis.

Keywords: Cystic fibrosis; Triple therapy; Modulators; Children; Adolescents

Abbreviations: ADHD: Attention-Deficit/Hyperactivity Disorder; AEs: Adverse Effects; CF: Cystic Fibrosis; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator; ETI: Elexacaftor/Tezacaftor/Ivacaftor

Introduction

Triple therapy with the CFTR (cystic fibrosis transmembrane conductance regulator) modulators elexacaftor/tezacaftor/ivacaftor (ETI) was approved in 2019 for all patients with cystic fibrosis (CF) aged 12 years and older who carry the F508del mutation [1]. Following the introduction of this therapy, multidisciplinary teams managing CF patients have observed substantial improvements in survival, quality of life, lung function, nutritional status, and pancreatic function [2,3]. Currently, both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved the use of ETI therapy for CF patients aged two years and older, a move that could potentially benefit more than 90% of the global population affected by this disease. ETI therapy is considered safe for pediatric patients with CF; however, adverse events (AEs)—such as transaminase abnormalities, skin rashes, poor gastric tolerance, and disturbances in sleep, behavior, and mental health—have been reported [4-6]. Furthermore, the multi-organ involvement associated with CF frequently can lead to mental health comorbidities that impact patients' quality of life, explaining why reports of AEs have generated concern and

interest among researchers and clinicians [7,8]. This mini-review documents key studies reporting on the favorable or unfavorable mental health effects observed following the implementation of ETI therapy in children and adolescents with CF.

Discussion

A study involving 197 preschoolers aged 2 to 5 years who initiated ETI therapy showed that, after one month of treatment, 47% experienced sleep or behavioral problems—disturbances that were absent at the start of therapy in 85% of these patients. The authors proposed several hypotheses for this finding: passage of the modulator across the blood-brain barrier with stimulation of CFTR present in certain areas of the central nervous system, activation of glial cells via the gut-brain axis, or binding to specific receptors in emotional processing areas [9]. A retrospective observational study of patients with CF aged 9 to 17 years reported a 17% prevalence of attention deficit hyperactivity disorder (ADHD) before starting ETI therapy. At the initiation of ETI therapy, 46% of the children with ADHD were receiving medication for the condition; after one year of

ETI therapy, this figure rose to 59%. The authors postulate that the increase in physical activity following ETI therapy might have been interpreted as hyperactivity, thereby influencing the increase in medication use [10].

In a 5-year follow-up study involving children and adults receiving ETI therapy, adverse events were reported in 19% of patients aged 6 to 18 years after initiating treatment, with psychiatric issues being the most common in this age group [11]. A prospective observational study demonstrated that children with CF treated with CFTR modulators had lower anxiety scale scores than those who did not receive this therapy. Furthermore, parents of children treated with CFTR modulators recorded lower scores on anxiety and depression scales than parents of children with CF who did not receive the treatment [12]. Another prospective study measured mental health symptoms over 18 months in children and adolescents aged 8 to 17 years who began ETI therapy, showing no increase in anxiety or depressive symptoms [13]. A review of 12 clinical studies involving adolescents aged 12 years and older and adults demonstrated that depression-related symptoms or events occurring after the initiation of ETI therapy were consistent with the background prevalence in cystic fibrosis, with no causal association found with the therapy [14].

A longitudinal study involving a cohort of adolescents over the age of 12 and adults who initiated ETI therapy demonstrated some improvements in biopsychosocial health and depression scores; however, these differences were not significant in the group under 25 years of age, nor in patients with a forced expiratory volume in one second (FEV1) <70%, women, or those using psychotropic medications prior to starting therapy [15]. Finally, another prospective longitudinal study with 15 months of follow-up, conducted solely with adolescents aged 10 to 18 with CF who initiated ETI therapy, showed no significant improvements in anxiety, depression, or sleep-related problems [16].

Conclusion

Research reporting on the impact of ETI triple therapy on the mental health of children and adolescents with CF presents conflicting findings. While some studies report disturbances in behavior, sleep, or mental health, others show an improvement in these symptoms or no effect on the mental health of children or adolescents with CF. Current evidence does not support a general recommendation to discontinue ETI therapy upon the emergence of mental health-related adverse events; such cases must be evaluated individually in consultation with the multidisciplinary treatment team. Further longitudinal studies are needed to establish causality regarding the positive or negative effects of ETI triple therapy on the mental health of children and adolescents with CF.

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DOI: [10.19080/IJOPRS.2026.07.555747](https://doi.org/10.19080/IJOPRS.2026.07.555747)

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