Case Report

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Coenzyme Treatment of Childhood and Adolescent Depression: A Case Series

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Abstract

Pediatric depression remains a treatment challenge, not only because of its increasing prevalence over the past year, but the "black box warning," which elaborates the possibility of suicidal thoughts or behaviors associated with antidepressant use in younger patients. We report a case series of pediatric patients, the majority of whom achieved remission of their depressive illnesses utilizing B vitamin-based coenzymes as monotherapy, and some of whom required an antidepressant medication added to daily coenzymes as adjunctive therapy. No patient reported side effects, and none reported an increase in suicidal thoughts utilizing B-vitamin-based, coenzyme therapy. The authors believe further study is needed to explore this safe treatment option for some of our most vulnerable patients.

Keywords: Depression; Pediatric; Childhood; Adolescence; Antidepressant; Treatment; Coenzyme; Vitamins

Introduction

The occurrence of major depression is increasing in our pediatric population. Prior to the COVID-19 pandemic, the rate of major depression was 1% to 2% annually for patients up to age 13, with an increasing prevalence through adolescence, reaching up to 7% by age 15, and the lifetime prevalence of depression has been estimated to be as high as 25% by the end of adolescence [1,2]. Further, suicide remains the second leading cause of death for individuals from ages 10 to 24 [3]. During the past year, the COVID-19 pandemic seems to have disproportionality affected our youths. Immediately following the first COVID-19 lockdowns, depressive disorders in pediatric patients increased exponentially. In March and April of 2020, mental health claims for patients aged 13-18 doubled over the same months in 2019. Further, and more worrisome, "intentional self-harm claims" for teens increased 91 percent in March 2020, compared with 2019. The increase was even larger when comparing April 2020 to 2019, with self-harm incidents essentially doubling (increasing 99.83 percent). For this same age group (ages 13-18), claims for overdoses increased 119.31 percent in April 2020 compared with April 2019 [4,5].

These alarming trends are further complicated by the ongoing treatment challenges in this vulnerable population. Researchers have noted unusually high placebo response rates, up to 60%, in some pediatric MDD trials [6]. Studies also indicate that pediatric patients tend to respond early in treatment, and further gains are minimal after 4 weeks of therapy. Unlike many of our adult patients, dose escalation in non and partial responders is less likely to result in remission [7]. Another concern is "pediatric behavioral activation syndrome." This cluster of side effects, involving irritability, activation, and insomnia, presents on a spectrum of severity, and is usually associated with pediatric patients, who, for metabolic reasons, experience higher than expected plasma levels of the antidepressant medication [8].

And, for nearly 17 years, clinicians have educated patients and parents on the controversial "black box" warning, which involves a possible increase in suicidal thoughts and self-harm behaviors, for those ages 24 and undertaking antidepressants. This warning led to an immediate and drastic reduction in treatment, and a subsequent 14% increase in teen suicides [9]. At present, only fluoxetine and escitalopram are FDA indicated for the pediatric population, and all antidepressant, some antipsychotics, and most anticonvulsants, are also associated with the "black box" warning regarding suicidality.

Clearly there is a need for safe alternatives to standard medications for our youngest patients. We report the use of EnLyte, a vitamin-based "coenzyme therapy," in twenty-two children and teens with major depression. Progress was measured using the Montgomery–Åsberg Depression Rating Scale (MADRS) at each visit. The MADRS is a ten-item observer-rated depression

scale, widely used in depression trials. Eleven of our patients achieved a full remission utilizing coenzyme monotherapy. Seven patients achieved remission when an antidepressant was added to coenzyme therapy, and four failed to fully respond to monotherapy, or combination coenzyme-antidepressant therapy.

EnLyte gel-caps contain nutritional supplements, including three forms of folate, and B vitamins in their metabolized forms. EnLyte is indicated for adults with MDD, and it is designed to allow for immediate CNS usage of folates, other B vitamins, and coenzymes. This agent thereby circumvents the suboptimal metabolism of various B vitamins, which is the principle genetic vulnerability leading to depressive disorders [10]. Because metabolized B vitamins are necessary coenzymes for the production of monoamines, EnLyte addresses the infinite variety of genetic polymorphisms associated with suboptimal monoamine synthesis. The manufacturer elaborates: EnLyte "is intended to address the increased need for metabolically-active forms of folate in the cerebrospinal fluid," and "may be useful in patients at risk of depression due to a deficiency of folate and/or cobalamin" [11].

Consistent with adult trials of EnLyte for MDD, no patient in our case series reported significant side effects, nor new-onset suicidal thoughts or behaviors from coenzyme treatment.

Case Presentation

Coenzyme monotherapy

Case 1: A 5-year-old female reported disturbingly homicidal obsessive-compulsive imagery, and vocalization of these images brought her to healthcare attention. She initially engaged in cognitive therapy, which failed to impact her OCD symptoms. She began n-acetylcysteine at 600 mg daily, which reduced the images by approximately 50%, but she further developed depressive symptoms. She soon reported thoughts of self-harm, and MADRS score was 24.

She was prescribed EnLyte, one daily, while continued on n-acetylcysteine. After six weeks, she reported a full resolution of depressive symptoms (MADRS of 8). Depression remains in remission six months after initiation of EnLyte therapy (MADRS of 6).

Case 2: An 8-year-old female was struggling academically and reporting stressors from her parents' divorce. MADRS was 22 at the initial visit. Her parents canceled a return visit with her initial clinician, who recommended sertraline, after they researched the standard suicide warning. Our clinic prescribed EnLyte, one daily, and at a two weeks, the patient showed some improvement but had plateaued by week four (MADRS of 16). Her dose was increased to twice daily, and three weeks later, she was in remission (MADRS of 6). She remains on EnLyte, approximately two years after her initial presentation.

Case 3: A 10-year-old male presented with major depression of moderate severity with a MADRS score of 21. He reported struggling with schoolwork and difficulty relating to peers. He had been prescribed methylated folate at 15 mg daily, but after two weeks, the agent was discontinued due to irritability. Our clinic prescribed EnLyte, one gel cap per day. Approximately three weeks later, he reported symptomatic improvement, with a MADRS of 14. Six weeks after presentation, he reported remission, with a MADRS of 5.

Case 4: A 13-year-old female reported several weeks of dysphoria, frustration with social issues at school, deteriorating grades, and a MADRS of 21. Daily EnLyte and cognitive therapy during med checks resulted in a MADRS score of 12 at four weeks, decreasing to 5 by week seven. She remained in remission for the duration of the school year, discontinued EnLyte during the summer.

Case 5: A 10-year-old male in foster care reported recurrent thoughts of death, chronic dysphoria, poor motivation, and failing grades (MADRS was 21 at presentation). Previous trials of fluoxetine (20 mg) and sertraline (50 mg) were not successful. EnLyte, once daily was prescribed, and MADRS score improved to 14 by week three, and to 6 by week eight. He had been referred for individual therapy after his second visit, and both therapies are ongoing for one year.

Case 6: A 16-year-old female with premenstrual dysphoric disorder and one depressive episode requiring hospitalization at age 14, presented with a MADRS of 25. Prior medication trials included escitalopram, 10 mg per day, with adjunctive lithium, 150 mg/day, which achieved remission. She declined the regimen during this relapse, citing past side effects (GI upset and headache). After three weeks of EnLyte, she requested an increase in dose, noting only modest benefit (MADRS of 21). At week eight, her MADRS was 9, and by week twelve she was in remission (MADRS 7). She remains on twice daily EnLyte, two years after presentation.

Case 7: A 14-year-old male had been treated for ADD with past stimulants. A recent unsuccessful trial of omega-3 supplementation led to despondency, school avoidance, and insomnia. When prescribed EnLyte daily, MADRS score was 24. He attended therapy for two visits but declined to return, failing to make a connection with the therapist. However, after five weeks, he reported some improvement (MADRS 18), and his dose was doubled. At three and a half weeks after the dose escalation, his MADRS was 6. He remains on EnLyte, twice daily, two years after presentation.

Case 8: A 17-year-old, who had taken paroxetine for PMDD, experienced withdrawal symptoms after discontinuing the agent. She was hesitant to resume antidepressant medications after presenting with depression, and a MADRS of 20.

Grades remained generally good, and social functioning remained baseline, although the patient elaborated she was "putting on a happy face". She was prescribed EnLyte daily, and within three and a half weeks her MADRS score dropped from 20 to 6. She remained on the agent until transitioning to another clinic out-of-state and was lost to follow up six months after her presentation.

Case 9: A 16-year-old, who had broken up with her boyfriend, overdosed on ibuprofen. After an emergency room evaluation, her subsequent outpatient visit revealed no suicidal thoughts or intent, but continued depressive symptoms (dysphoria, ruminations, poor concentration, and hypersomnia). MADRS was 21, and she was prescribed EnLyte, once daily. At week four, MADRS was 7, and she remains euthymic, seven months after her initial presentation.

Case 10: A 12-year-old female, with a significant family history of affective illness, developed major depression after her mother's fatal opiate overdose. The patient, living with her grandparents, rebelled against limits on screen-time, was irritable at home and school, and refused to help with household chores. Prior to the death of her mother, she was an honor roll student, yet only one grade was passing at the time of presentation. MADRS at presentation was 22. She was prescribed EnLyte, once daily, and continued in individual therapy every two weeks. After seven weeks of EnLyte and continued therapy, she reported a resolution in the majority of her symptoms (MADRS of 14), but irritability and oppositional behavior were still prominent. By week nine, her MADRS was 8, and though not fully resolved, her oppositional behaviors improved significantly, and grades had improved to A's.

Case 11: A 17-year-old female, the victim of sexual abuse with PTSD symptoms, presented with depression, suicidal thoughts, and cutting behaviors. The patient believed that a trial of escitalopram may have contributed to an increase in intrusive, negative (but not suicidal) thoughts. This was followed by a trial of fluoxetine which caused "emotional numbing," and she was hesitant to begin another medication. MADRS was 19. EnLyte was prescribed, as was prazosin (2 mg at bedtime), for nightmares. After eight weeks of individual therapy and EnLyte, MADRS was 7. She reported neither emotional numbing, nor a recurrence of suicidal thoughts. She remains stable at fourteen months.

Combination coenzyme/antidepressant therapy

Case 12: A 17-year-old female was active in school sports until developing major depression. She quit her team, and grades deteriorated. Symptoms included tearful episodes, anxiety, anhedonia, poor concentration, and she believed depression had prompted difficulties with her attention span. She was prescribed amphetamine salts, 10 mg twice daily, by her pediatrician, and noted some benefit in ADD symptoms, but continued to report depression. MADRS was 25 at presentation. EnLyte was prescribed daily, and the patient reported mild benefit at a four-week follow-up visit. The dose was doubled to twice daily, yet only mild benefit was noted (MADRS of 21). She was then prescribed escitalopram, 10 mg daily. With this combination her MADRS score had dropped to 6 by week four. She also remains on amphetamine salts, but the dose has been lowered to 5 mg twice daily due to irritability on initial dosing.

Case 13: A 7-year-old boy reported sadness and isolation after a family move took him away from neighborhood friends. Difficulty finding friends in his rural community, and academic struggles led to depression. He presented with a MADRS of 17, and was started EnLyte therapy, once daily. He further met with an individual therapist for two visits. He responded partially by week six (MADRS of 14). Fuoxetine, 10 mg every other day (at parent request), was added, and by the third week of combination fluoxetine-EnLyte therapy, his MADRS was 8. He remains stable five months after presentation.

Case 14: A 17-year-old patient was struggling with depressive symptoms through his senior year, with no significant stressors identified. His grades had dropped to C/D levels, and he reported anhedonia, apathy, dysphoria, and thoughts of self-harm without plans or intent. EnLyte, once daily, was prescribed. The patient's MADRS dropped from 27 to 19 in six weeks. Though improved, he remained in the depressive episode. He was referred, over spring break, for induction of esketamine treatment. He was administered 28 mg by nasal spray twice a week for four weeks, then weekly for two more weeks while continuing EnLyte. At this point, he noted a full resolution of symptoms. He remains on a maintenance dose of one EnLyte per day, and is relapse free at seven months.

Case 15: A 15-year-old male reported a history of major depression, and one prior hospitalization due to suicidal thoughts and intent. He responded to fluoxetine, 20 mg daily, but reported emotional numbing and bizarre dreams. He discontinued fluoxetine, and despite individual therapy every three to four weeks, suffered a relapse. He honored his safety contract, and sought help four months after discharge when suicidal intent recurred (MADRS was 22). EnLyte was prescribed daily. Individual therapy continued, and by week seven, his MADRS was 15. By week twelve, he was prescribed liquid fluoxetine, 5 mg a day, and prazosin 2 mg at bedtime to suppress dreams. By week fifteen, with this new combination of EnLyte, fluoxetine, and prazosin, he was in remission (MADRS of 7).

Case 16: A 13-year-old came to our attention after his school counselor recommended medication management for new onset depression. Stressors included family discord and challenges with certain classes. He was started on fluoxetine, 10 mg a day, and achieved a partial response. MADRS decreased from 18 to 14 after six weeks. He declined individual therapy but began EnLyte daily. After three weeks of fluoxetine and EnLyte, he achieved full remission (MADRS of 6).

Case 17: A 6-year-old male, who had begun alternating residences after his parents' separation, became irritable and was apathetic towards schoolwork, and refused to attend school intermittently. His therapist referred him for medication evaluation. At presentation, his MADRS was 18, and he endorsed passive suicidal thoughts (wishing he would not wake up each morning). He was prescribed EnLyte daily, and modest improvement was noted in four weeks (MADRS of 15). Fluoxetine was started at 10 mg daily, and within one week, irritability had resolved. After three weeks of this regimen, MADRS was 8. The patient remains in remission at six months.

Case 18: A 17-year-old female required hospitalization for

depression at age 15, and was treated with fluoxetine. She had been off medication for one year when she presented with a MADRS of 20, reporting no precipitating stressor. She had a strong family history of MDD (mother, and both grandmothers). Her parents resisted the initiation of an SSRI, and she was prescribed EnLyte. She saw a reduction in MADRS from 20 to 14 by week five, and due to lack of full response, vortioxetine, 5 mg daily, was added. After four weeks of this combination, the patient achieved remission, with a MADRS of 6.

Non-responders/treatment-resistant cases

Case 19: A 16-year-old reported two prior suicide attempts resulting in hospitalizations. He had failed to respond to fluoxetine, duloxetine, sertraline (augmented with buspirone), and lamotrigine (augmented with lithium). He presented with a MADRS of 29 while taking venlafaxine, 75 mg daily. His parents refused the option of dose escalation. Daily EnLyte was added, and there was modest benefit by week two. The dose was escalated to twice daily at family request; however, the benefit remained modest (MADRS of 24). As suicidal ideation continued, his parents sought TMS therapy. This was administered with the continued regimen of venlafaxine 75 mg daily, and EnLyte twice daily. Family reported that he was no longer suicidal, but far from remission. He was then referred for ECT, with again, modest benefit: A MADRS of 18 was noted after twelve unilateral treatments.

Case 20: A 16-year-old male with depression reported unsuccessful trials of fluoxetine and sertraline, and moderate success with vilazodone. He had not achieved remission over the past two-and-a-half years, and presented with a MADRS of 19. He was started on EnLyte daily, and by week three reported no benefit. His dose was escalated to twice daily. He continued to report no benefit at week eight, and sought transcranial magnetic stimulation treatment. Though TMS in combination with EnLyte lacked any side effects, it was not successful, and the family was seeking other options when lost to our care.

Case 21: An 11-year-old, reported cyber and in-person bullying, was referred for medication management by her individual therapist. She was prescribed EnLyte daily, and her MADRS score by week three had dropped from 22 to 18. At week six her mother requested a trial of fluoxetine. The patient was prescribed 10 mg daily, and after four weeks, her MADRS was 17. She failed to achieve full remission but remained in individual therapy, without suicidal thoughts. Though she has not achieved remission (MADRS of 15), she has been on combination therapy for nine months.

Case 22: A 15-year-old female with a history of recurrent depression, past sexual abuse, and cutting behaviors, reported chronic dysthymia, and a prior partial response to a combination of lamotrigine and fluoxetine. At presentation, MADRS was 19, and she endorsed suicidal thoughts. She had been lost to individual therapy for sixteen months at the time of presentation. She failed to respond to EnLyte monotherapy at four weeks, the addition of sertraline (50 mg daily for four weeks, then 100 mg daily), and further, to lithium augmentation. The patient consequently required hospitalization when self-harm behaviors escalated. Her MADRS had increased from 19 to 21 by hospitalization.

Discussion

The traditional approach to pediatric depression has been standard antidepressant medication, and when indicated and possible, medication is combined with cognitive-behavioral therapy. However, standard antidepressant medications involve warnings, concerns regarding efficacy, and various potential side effects.

Unlike traditional medications, which can only block the re-uptake of neurotransmitters believed to be in short supply in MDD, coenzyme therapy enables the CNS to manufacture adequate monoamines by addressing the root, and genetic causes of MDD. Vitamin-based coenzyme therapy is designed to circumvent the great variety of possible genetic polymorphisms associated with “one-carbon metabolism” or homocysteine (HCY) metabolism in the CNS, and all other associated genetic variants that may alter monoamine synthesis. The presence of genetic variants that result in suboptimal methylation is the basis of the “homocysteine theory of depression” [10].

The homocysteine theory argues that, for each patient, a unique cluster of genetic vulnerabilities will result in, not only inadequate monoamine synthesis, but a baseline condition of elevated CNS HCY, impaired methylation of DNA, suboptimal antioxidant production, and impaired hormonal signaling. Thus, the homocysteine theory is ultimately a unifying theory of depression, as it accounts for all known hypotheses: genetic, hormonal, inflammatory, and monoamine. A unique set of polymorphisms may not be clinically significant at baseline, yet disease may manifest in times of psychosocial or environmental stress (prompting depressive episodes, PTSD, or adjustment disorders). It has recently been established that patients who experience childhood trauma and subsequent depression are more likely to test positive for one of the many possible methylenetetrahydrofolate reductase (MTHFR) polymorphisms [12]. MTHFR facilities the last enzymatic step in folate metabolism, and the functional capacity of MTHFR is the primary determinant of CNS HCY levels [10].

The coenzymes necessary for HCY metabolism and monoamine production include metabolized B vitamins, micronutrients, and other enzymes and coenzymes which are dependent upon metabolized B vitamins for their synthesis. Though few of our patients suffer from low vitamin intake, B vitamins require adequate absorption and full metabolism to function as coenzymes.

We will never know the exact combination of polymorphisms that exist in each patient that result in deficiencies of vitamins metabolism, or the extent of influence for each of these numerous possibilities, particularly since polymorphisms exist to various degrees of severity (making the combinations essentially infinite). However, we can supply the CNS with all the necessary

Table 1: Cone Health coenzyme algorithms for pediatric depression.

Mild-moderate MDD	Severe MDD
Coenzyme therapy+CBT	Coenzyme+SSRI+CBT
No/partial response in 3-4 weeks	No/partial response in 3-4 weeks
Increase to BID Coenzyme dosing-No/ partial response in 3-4 weeks	Increase to BID coenzyme therapy-No/ partial response in 3-4 weeks
Add SRI-No/partial response in 3-4 weeks	Increase or change antidepressant-No/partial response in 3-4 weeks
Increase or change antidepressant-No/partial response in 3-4 weeks	Explore other adjunctive therapies and/or 3rd/ 4th line measures
Explore 3rd and 4th line options	

coenzymes associated with monoamine synthesis. The current products designed to provide B-vitamin based coenzyme therapy are trade-named EnLyte, EnLyte-D, and EnBrace HR.

In a double-blind placebo-controlled trial of MDD patients with MTHFR polymorphisms, EnLyte monotherapy separated from placebo by week two. The remission rate with EnLyte monotherapy was 42% by week eight. Further, clinical improvement correlated with a significant reduction in homocysteine levels in a majority of responders [13]. EnBrace HR was recently studied in two groups of women: the first planned to discontinue antidepressants for pregnancy (and were in remission at entry). Group 2 included patients who developed MDD during pregnancy. EnBrace HR was shown in group 1 to prevent relapse through pregnancy and into the post-partum period, compared to a 63% relapse rate for those who discontinued antidepressants and did not receive EnBrace HR. For group 2, EnBrace HR was efficacious for the treatment of acute depression during pregnancy, with a 100% remission rate by week two, with an average MADRS score of 26 decreasing to 8 [14].

The Coenzyme Algorithms utilized in Cone Healthcare system for pediatric patients with depression are elaborated in **Table 1**. Patients with mild to moderate depression should begin with a trial of coenzyme gel-caps. If response is lacking or partial, the dose may be doubled, as there is great patient-to-patient variance in coenzyme absorption. If partial or nonresponse is still noted, after at least 3 weeks, a low dose of fluoxetine or escitalopram may be added as adjunctive therapy. If a patient presents with severe depression, we recommend the coadministration of an antidepressant medication and co-enzyme therapy.

Conclusion

The authors believe that vitamin-based coenzyme therapy should be considered first-line agents for youth with mild or moderate depressive disorders, and standard antidepressant medication should be used adjunctively in partial and non-responders, or combined with coenzyme therapy from the outset in severe cases. Though we look forward to placebo-controlled trials of coenzyme treatment in the pediatric population, the safety of vitamin-based option justifies their current use as initial treatment.

Vitamin-based coenzyme therapy offers the advantage of safety while addressing the genetic, root cause of depression. The authors were pleased with the overall response to this strategy, and emphasize that patients failing a combination of coenzyme-antidepressant therapy, also proved treatment-resistant to third, and fourth-line measures. No patient complained of side effects, nor had an increase in suicidal thoughts or impulses.

References

1. Kessler RC, Avenevoli S, Ries Merikangas K (2001) Mood disorders in children and adolescents: An epidemiologic perspective. Biol Psychiatry 49: 1002-14.
2. Lewinsohn PM, Rohde P, Seeley JR (1998) Major depressive disorder in older adolescents: Prevalence, risk factors, and clinical implications. Clin Psychol Rev 18: 765-94.
3. Centers for Disease Control and Prevention (2015) National Vital Statistics System. Deaths, Percent of Total Deaths, and Death Rates for the 15 Leading Causes of Death in 5-year Age Groups, by Race and Sex: United States, 1999-2015.
4. Racine N, Cooke JE, Eirich R, Korczak DJ, McArthur B, et al. (2020) Child and adolescent mental illness during COVID-19: A rapid review. Psychiatry Res 292: 113307.
5. FAIR Health (2021) The impact of Covid-19 on pediatric mental health.
6. Walkup JT (2017) Antidepressant efficacy for depression in children and adolescents: Industry and NIMH-funded studies. Am J Psychiatry 174: 430-437.
7. Varigonda AL, Jakubovski E, Taylor MJ, Freemantle N, Coughlin C, et al. (2015) Systematic review and meta-analysis: Early treatment responses of selective serotonin reuptake inhibitors in pediatric major depressive disorder. J Am Acad Child Adolesc Psychiatry 54: 557-64.
8. Reinblatt SP, DosReis S, Walkup JT, Riddle MA (2009) Activation adverse events induced by the selective serotonin reuptake inhibitor fluvoxamine in children and adolescents. J Child Adolesc Psychopharmacol 19: 119-26. 10.1089/cap.2008.040.
9. Garland EJ, Kutcher S, Virani A, Elbe D (2016) Update on the use of SSRIs and SNRIs with children and adolescents in clinical practice. J Can Acad Child Adolesc Psychiatry 25: 4-10.
10. Farah A (2015) Inadequate homocysteine metabolism: A theory of depression. Psychiatric Annals 45: 469-472.
11. EnLyte (2019) Sunset, LA: Jaymac Pharmaceuticals.
12. Lok A, Bockting C, Koeter M (2013) Interaction between the MTHFR C677T polymorphism and traumatic childhood events predicts depression. Transl Psychiatry 3: e288.
13. Mech AW, Farah A (2016) Correlation of clinical response with homocysteine reduction during therapy with reduced B vitamins in patients with MDD who are positive for MTHFR C677T or A1298C polymorphism: A randomized, double-blind, placebo-controlled study. J Clin Psychiatry 77: 668-71.
14. Freeman MP, Savella GM, Church TR, Góez-Mogollón L, Sosinsky AZ, et al. (2019) A prenatal supplement with methylfolate for the treatment and prevention of depression in women trying to conceive and during pregnancy. Ann Clin Psychiatry 31: 4-16.