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# Targeting the Endocannabinoid System in the Treatment of ADHD

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## ABSTRACT

*Dysfunction of the dopamine system has been proposed to explain clinical manifestations of ADHD. ADHD patients have been demonstrated to lack appropriate dopamine levels. The neurotransmitter dopamine is commonly associated with the brain's pleasure system, providing a feeling of enjoyment and motivation to perform specific tasks. The endocannabinoid system has been implicated in various dopamine-deficiency-related disorders, including ADHD. A complex interaction between the endocannabinoid system and dopamine production has been experimentally demonstrated. The endocannabinoid primarily responsible for the release of dopamine is anandamide and increasing the concentrations of this molecule has demonstrated therapeutic value in treating ADHD. In this review article, synthetic and natural exogenous and endogenous methods for increasing anandamide concentrations are described.*

## Keywords

ADHD, Endocannabinoid system, Endocannabinoid deficiency disorder, Anandamide, Dopamine, Serotonin, Phytocannabinoid, Pharmaceutical, Nutraceutical, FAAH inhibitor, Biochanin A, Behavior Genetics, Molecular Genetics, Biomolecular Psychology, FDA.

## Introduction

Attention deficit hyperactivity disorder (ADHD) is a term used for a group of behavioral symptoms, which include inattentiveness, hyperactivity, and impulsiveness. ADHD is not usually diagnosed until six to twelve years of age. It affects around 5% of children and 3% of adults worldwide [1]. The disorder is characterized by developmentally inappropriate and impairing levels of inattention, hyperactivity, and impulsivity, commonly accompanied by emotional dysregulation, cognitive impairments, and psychiatric comorbidities [2]. Behavior genetics, molecular genetic studies, and biomolecular psychology have converged to demonstrate both genetic and nongenetic factors contribute to the development of ADHD [3]. Family, twin, and adoption studies compellingly demonstrate that genes significantly mediate susceptibility to ADHD. These gene studies of ADHD have produced substantial evidence implicating several genes in the etiology of the disorder.

## ADHD as an Endocannabinoid Deficiency Disorder

Human and animal studies have consistently demonstrated the endocannabinoid system is fundamental for emotional homeostasis and cognitive function [4]. All vertebrates possess a measurable endocannabinoid tone reflecting concentrations of anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which have been categorized as centrally acting endocannabinoids, and their decreased concentration shows a significant correlation to the development of a variety of physical and psychological disorders [5]. Deficiencies of different endocannabinoid system elements contribute to the pathophysiology of several mental disorders, with varying alterations in gene and protein expression of CB1 receptors being demonstrated, depending on the technical approach used or the brain region studied [4].

The endocannabinoid system has been implicated in various dopamine-deficiency-related disorders, including ADHD, autism, schizophrenia, Parkinson's disease, and Huntington's disease. [6-13]. A complex interaction between the endocannabinoid system and dopamine production has been demonstrated experimentally, displaying the dysfunction of the dopamine system as a proposed explanation of the clinical manifestations of ADHD [14].

## Pharmaceutical Approaches to Treating ADHD

Typically, the first course of treatment for ADHD is a prescription for an amphetamine (Adderall) or methylphenidate (Ritalin). Dexedrine is twice as potent as Ritalin, a better-known stimulant, and second only to Ritalin in treating ADHD. However, because the PDR lists Dexedrine under "Diet Control" medications, many insurance companies will not cover Dexedrine to treat ADHD [15]. While all these pharmaceutical options are addictive and produce a host of unpleasant side effects involving the cardiovascular and central nervous systems, gastrointestinal problems, pituitary dysfunction, blood pressure problems, anxiety, headaches, delayed growth, and nausea, they are considered viable treatment options because they activate the release of dopamine, the key chemical in the brain's reward center [16]. Dopamine is commonly linked with the brain's pleasure system, providing a feeling of enjoyment and motivation to perform specific tasks [17]. ADHD patients have been confirmed to lack appropriate dopamine levels, which allows for the experience of a sense of reward and motivation [18]. An overwhelming body of neurochemical evidence unequivocally demonstrates that specific phytocannabinoids increase anandamide concentrations, the endocannabinoids responsible for releasing dopamine [19-24]. Since the discovery of the endocannabinoid system in 1992, extensive anecdotal evidence, survey data, research studies validate that increasing the level of the endocannabinoid anandamide can directly help with not only the side effects of Adderall but also symptoms of ADHD through the direct release of dopamine [20,24-25].

## Second Line of Pharmaceutical Medications

While stimulants are the first-line medication in the psychopharmacological treatment of attention-deficit hyperactivity disorder, 10% to 30% of all children and adults with ADHD either do not respond well, or do not tolerate treatment with stimulants, or demonstrate adverse side effects that are pharmacologically treated with antidepressants such as Zoloft, Paxil, and Prozac [27]. Atomoxetine was the first non-stimulant approved for treating ADHD in the United States by the Food and Drug Administration and is marketed as a good alternative for people who cannot tolerate or do not experience the desired effects of stimulant medications. However, there are critical safety concerns about this ADHD drug being implicated in sudden cardiac death and suicidal behavior [27].

## Competing Approaches for Treating ADHD

Pharmaceutical and nutraceutical approaches for enhancing dopamine levels to treat ADHD compete in remarkable ways. Pharmaceuticals have the disadvantage of iatrogenic effects, often resulting from the body's inability to degrade the synthetic molecules of which they are composed. The psychotropic effects produced by synthetic amphetamines have the advantage of claiming FDA approval. Nutraceuticals have the advantage of being natural, providing them some biomolecular superiority. Because they are natural, nutraceuticals have the disadvantage of being unpatentable and cannot be considered for FDA approval [28]. Since the FDA's inception, the public has been conditioned to accept FDA approved medications are safe; however, this perception is being questioned as adverse effects of FDA-approved treatments are increasingly exposed [29].

Shortly after the endocannabinoid system was discovered, Fatty acid amide hydrolase (FAAH) was demonstrated to be the enzyme that degrades anandamide, the dopamine-releasing endocannabinoid [30]. At that time, molecular engineers began studying FAAH as a target for pharmaceuticals because controlling FAAH levels may yield some of the same health effects that excite clinicians about the potential for phytocannabinoid-based medicines. Synthetic cannabinoids work by inundating the system with molecules structurally similar to THC and other phytocannabinoids [31]. Medicines that inhibit the body's manufacture of FAAH are confirmed to have a comparable effect by exploiting the level of deficient endocannabinoids in the central nervous system. If the deficiency is in anandamide, reduced FAAH results in increased concentrations of anandamide [29].

## Adverse Effects of Synthetic FAAH Inhibitors

Raising the endocannabinoid concentrations by impeding FAAH and additional catabolic enzymes, rather than controlling exogenous agents, is conjectured to reduce cannabinoid-like adverse events attributed to the intromission of a particular phytocannabinoid [32]. Synthetic FAAH inhibitors display neurological side effects not manifested by the biologic, including impairment of cognition, motor functions, and a predisposition to psychoses, especially when these agents are used for long-term treatment [1,33].

The creation of potent and safe synthetic FAAH inhibitors has been hindered by their harmful side effects [34]. On July 9, 2015, Biotrial research organization initiated human test trials of the synthetic FAAH inhibitor BIA 10-2474 by recruiting 128 healthy volunteers, consisting of men and women aged 18 to 55 [35]. The study involved a three-stage design, with 90 participants intromitting the medicine throughout the trial's initial stages. No serious adverse events were reported. The study participants stayed at Biotrial's treatment center for two weeks, undergoing tests, and the pharmaceutical was intromitted for ten days. Starting on January 7, 2016, six male volunteers received doses by mouth in the third stage. On January 10, the first volunteer was hospitalized, became brain dead, and died a week later. The other five volunteers were also hospitalized. Four suffered injuries, including severe necrotic and hemorrhagic lesions as displayed on brain MRIs. The trial was discontinued on January 11, 2016. Three of the four men displayed neurological indicators detrimental enough to paint a picture to fear that there would be an irreversible handicap even in the best scenario [35].

Magnetic-resonance-imaging scans revealed bleeding and dying tissue deep within the brain [35]. Many questions remain unanswered, particularly the biomolecular mechanism causing the participants' injuries. This clinical trial's devastating result led to a scramble of scientists suggesting various accounts as to the origin of the deadly adverse effects from the synthetic FAAH inhibitor. It has been proposed that the adverse effects may come from its binding to unknown off-targets. However, few methods exist to

foresee cellular off-target effects resulting from the drug binding to biological assemblies and their associations with diseases [36]. Due to the lack of understanding of the endocannabinoid system by scientists barred from learning about it in college, they missed the mark when attempting to explain what the off-targets of FAAH inhibitors might be and how these off-targets affect the system-level response [37].

## Degradation of Synthetic and Biologic FAAH inhibitors

FAAH inhibitors are designed to remove FAAH proportionally, thereby increasing the concentration of anandamide naturally produced by the body. Enough is now known about biomolecular psychology and the endocannabinoid system to hypothesize about the mechanism by which synthetic molecules cause neurological damage [29]. The side effects are likely not a byproduct of FAAH-inhibition directly, but rather the result of biologic enzymes being incapable of effectively degrading synthetic FAAH inhibitors. Biologic FAAH inhibitors demonstrate significant variances in their molecular composition compared with their synthetic counterparts [32]. The differences in the molecular structures may explain variances in the safety profiles between the artificial and the biological. These differences are related to the time it takes for the FAAH inhibitors to degrade. Information is deficient concerning what enzyme degrades synthetic or biologic FAAH inhibitors, and this is an area where further research is warranted (Figure 1). Technological restrictions, coupled with a suppression of research of biologic cannabinoids at many major research universities, have resulted in an inadequate understanding of the endocannabinoid system. A difference in these degradation rates would clarify the variance in adverse effects between biologic and synthetic FAAH inhibitors. Despite robust and well-accepted evidence regarding the efficacy of supplementing biologic cannabinoids to treat deficiencies of endocannabinoids, the application of this knowledge is still in its beginning stages [38-40].

## Comparing Pharmaceutical and Nutraceutical Approaches in Treating ADHD

What we know about manipulating endocannabinoid tone in the treatment of ADHD is elementary but somewhat convoluted. The endocannabinoid primarily responsible for the release of dopamine is anandamide (AEA), and increased levels of this molecule demonstrate therapeutic value [41]. While dopamine deficiency has long been known to be a significant contributor to ADHD manifestation, a chronic deficit of serotonin has also been shown to trigger symptoms of ADHD [42].

The synthetic approach provides two methods of increasing dopamine levels in subjects with ADHD, one exogenous (stimulants and amphetamines) and one endogenous (FAAH inhibitors). Both approaches result in undesirable side effects resulting from the

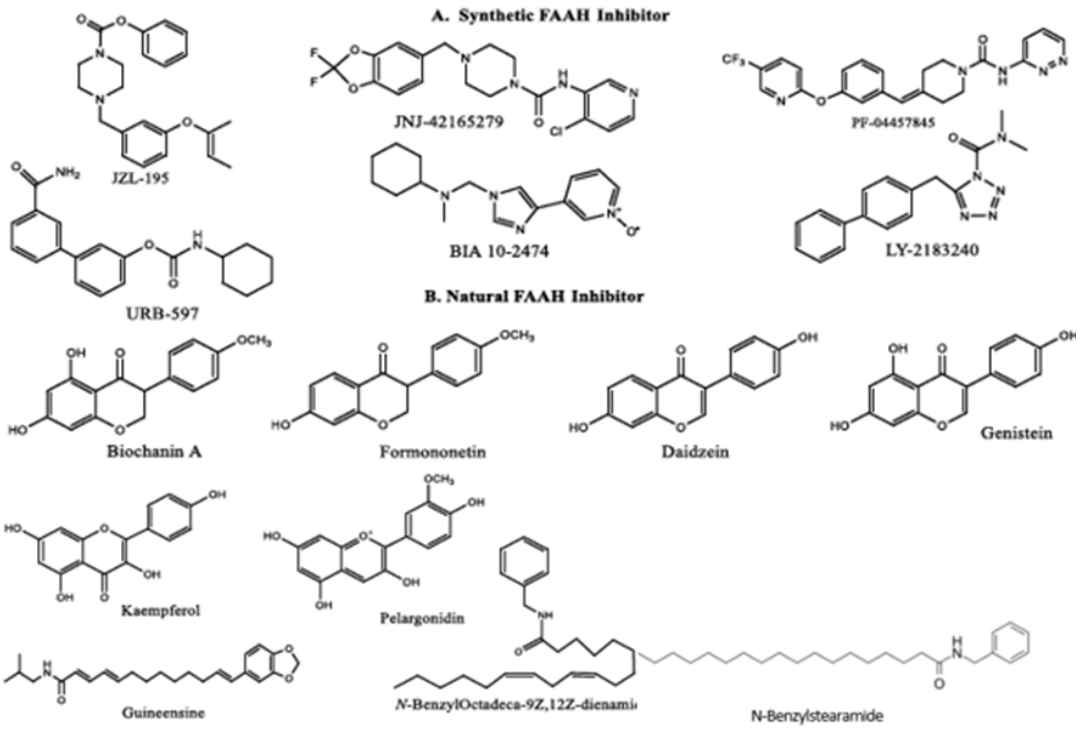


**Figure 1:** Chemical structures of Synthetic (A) and Naturally Occurring FAAH Inhibitors (B).
A) Selective and potent synthetic FAAH inhibitors. B) Chemical structures of naturally occurring FAAH inhibitors from various plant sources: Biochanin A, Formonetin, Daidzein, and Genistein (flavonoids found in red clover; Trifolium pretense), Myristicin (nutmeg, anise, parsley, dill), Kaempferol (broccoli, tomatoes, grapes, green tea), Pelargonidin (all berries, plums, pomegranates), Guineensine (alkaloid found in log pepper; Piper longum); Macamides N-Benzylstearamide and (N-BenzylOctadeca-9Z, 12Z-dienamide (Maca, Lepidium meyenii). Courtesy Jana Sharp.

body's inability to degrade them. The nutraceutical approach allows for exogenous and endogenous techniques for increasing dopamine, and the organic composition of biological molecules allows the body to efficiently degrade them, minimizing these adverse effects. Synthetic stimulants and amphetamines are thought to work because they increase dopamine levels exogenously, and synthetic FAAH inhibitors work by inhibiting anandamide's degradation in the nervous system, endogenously increasing the production of dopamine [32].

The nutraceutical methodology increases the production of dopamine in similar ways. The phytocannabinoids CBC, CBN, THC, and CBG activate anandamide receptors, thereby exogenously increasing dopamine concentrations, while CBD exogenously releases serotonin [43]. Natural FAAH inhibitors work endogenously by inhibiting the degradation of anandamide in the nervous system, thereby increasing dopamine production.

### Comparing Dosing Philosophies of Pharmaceutical and Nutraceutical CBD

Restrictive laws and limited funding create difficulties in conducting clinical dosing trials with biologic cannabinoids. Limited data is available on phytocannabinoids' safety profiles for both adults and children. A one-year study enrolled 214 children throughout the United States with treatment-resistant epilepsy where these children required multiple medications and were experiencing repeated breakthrough seizures [44]. These subjects were given CBD in huge doses of 25-50-mg/kg/day, much larger than typically needed to treat other disorders such as ADHD, anxiety, inflammation, or insomnia. Assuming the child was only 45 pounds, this dose is equivalent to 500-1000mg of CBD every day over the course of a year. This provides reassurance that if a dose of 1000-mg is safe for a child to take daily over one year, much lower doses are safe as well [44]. The U.S. Food and Drug Administration & the European Medicines Agency used this study to determine acceptable doses of CBD preparations for treating seizures in children with Dravet & Lennox-Gastaut syndromes while also approving CBD for use in neonatal asphyxia. This justifies to medical authorities in the United States & Europe the benefits CBD can offer the newborn and pediatric population outweighs the risks in doses up to 1000mg [44]. Most endocannabinoid deficiency and autoimmune disorders are effectively treated with much lower CBD doses than the 1000mg threshold. Physicians generally advise a 30-pound toddler to take 15-30 mg of CBD per day [45].

The nutraceutical approach to treating ADHD utilizes both an endogenous and exogenous approach, employing the phytocannabinoids CBC and CBG to increase dopamine levels exogenously and CBD to exogenously facilitate the release of serotonin. This approach also utilizes Biochanin A, a natural FAAH inhibitor, to endogenously increase dopamine levels by inhibiting the degradation of anandamide. Biochanin A is an isoflavone predominately found in red clover. It has exhibited various medicinal activity, including anti-inflammatory, estrogen-mimicking, glucose lipid modulatory activity, also cancer preventive and neuroprotective benefits [46-55]. Biochanin A is also a mixed-type inhibitor of FAAH, demonstrating low micro molar potencies towards the rat, mouse, and recombinant human FAAH, without the side effects generally related to its artificial counterparts. It has drawn extensive attention from researchers in recent years owing to the broad spectrum of its pharmacological action, many related to its activity as a natural inhibitor of fatty acid amide hydrolase. FAAH is the enzyme accountable for the metabolism (degradation) of the endogenous cannabinoid receptor ligand anandamide (AEA) and various other endogenous fatty acid amides, demonstrating a distribution consistent with its role in regulating their effects at their released sites of action. This is the mechanism responsible for the effectiveness Biochanin A exhibits in treating multiple endocannabinoid deficiency disorders, including Post Traumatic Stress Disorder, Autism, Attention-Deficit/Hyperactivity Disorder, Alzheimer's disease, Multiple Sclerosis, Dementia, Parkinson's disease, Huntington's disease, and scores of other nervous system disorders resulting from deficiencies in anandamide [55-57].

### Issues of Bioavailability

Biochanin A has drawn researchers' considerable attention due to its wide array of pharmacological actions, including its neuroprotective, anticancer, antioxidant, anti-inflammatory, osteogenic, and anti-hyperglycemic properties [57]. Even though this isoflavone's therapeutic potential is intriguing, it is considered limited due to its truncated oral bioavailability. As is frequently the case in scientific endeavors associated with biomolecular psychology, an innovative approach must be devised to adapt to this identified limitation. Biochanin A has low solubility, which interferes with its oral absorption [57]. While oral intromission is typical for nutraceuticals, a more effective method of ingestion has been developed. Transdermal patches distribute a specific dose of medicine into the bloodstream via a porous membrane. An advantage of a transdermal delivery system is that it delivers a measured release of the compound into the subject. Many pharmaceuticals are currently available in transdermal patch form, and this delivery method can readily be appropriated to enhance the bioavailability of nutraceuticals such as Biochanin A [57].

## Summary

Research has consistently demonstrated that the endocannabinoid system is fundamental for emotional homeostasis and cognitive functions correlating to the development of various physical and psychological disorders [4]. Behavior genetics, molecular genetic studies, and biomolecular psychology have converged to reveal both genetic and nongenetic factors contribute to the development of ADHD. Targeting the endocannabinoid system in treating ADHD exposes the dopamine system's dysfunction as a proposed explanation of the clinical manifestations of ADHD [14].

Current pharmaceutical options that treat ADHD, such as Ritalin and Adderall, are addictive and produce a host of unpleasant adverse events; however, they are considered viable treatment options because they activate the release of dopamine [15]. An astonishing 10% to 30% of all children and adults with ADHD either do not respond well or do not tolerate treatment with

stimulants nor display adverse effects. These side effects are treated with antidepressants, with Zoloft, Paxil, and Prozac being the most widely prescribed [16].

Research studies validate that increasing the endocannabinoid anandamide (AEA) level can directly combat the side effects of Adderall and symptoms of ADHD by the direct release of dopamine [25]. Ample neurochemical evidence unequivocally establishes that specific phytocannabinoids increase anandamide concentrations, the endocannabinoids responsible for releasing dopamine [19-24]. ADHD patients have been confirmed to lack appropriate dopamine levels, which allows for the experience of a sense of reward and motivation [25].

Nutraceuticals have the disadvantage of being unpatentable because they are natural and cannot be considered for FDA approval. The psychotropic effects produced by synthetic amphetamines have the advantage of claiming FDA approval. The public has been conditioned to believe "FDA approved" means safe, although this perception is becoming questioned, as adverse effects of FDA-approved medications are increasingly exposed [28].

Fatty acid amide hydrolase (FAAH) is identified as the enzyme that degrades anandamide, the dopamine-releasing endocannabinoid [29]. Medications that inhibit the body's production of FAAH are hypothesized to have a similar effect by increasing the concentration of deficient endocannabinoids in the central nervous system. If the deficiency is in anandamide, reduced FAAH results in its increased concentration [29].

Synthetic FAAH inhibitors exhibit neurological adverse events not manifested by the biologic, including impairment of motor functions, cognition, and a predisposition to psychoses, especially when these agents are used for long-term treatment [1,33]. The creation of potent and safe synthetic FAAH inhibitors has been hindered by their harmful side effects [34]. Scientists missed the mark when attempting to explain the off-targets of FAAH inhibitors and how these off-targets affect the system-level response [37].

Enough is now known of the endocannabinoid system and biomolecular psychology to theorize about the mechanism by which synthetic compounds cause neurological damage [32]. Information is lacking concerning what enzyme degrades either synthetic or biologic FAAH inhibitors. This is an area where further research is warranted. A difference in these degradation rates would clarify the variances in the synthetic and biologic FAAH inhibitors' adverse effects. The science regarding the efficacy of supplementing phytocannabinoids to treat endocannabinoid deficiency disorders is robust and well accepted; however, utilization of this knowledge is still in its infancy [38-40]. The synthetic approach provides two methods of increasing dopamine levels in subjects with ADHD, one exogenous (stimulants and amphetamines) and one endogenous (FAAH inhibitors). Both approaches result in undesirable side effects resulting from the body's inability to degrade them. A chronic deficit of serotonin has also been shown to trigger symptoms of ADHD [42].

The nutraceutical methodology increases the production of dopamine in similar ways. The phytocannabinoids CBC, CBN, THC, and CBG activate anandamide receptors, thereby exogenously increasing dopamine concentrations, while CBD exogenously releases serotonin [43]. The nutraceutical approach utilizes Biochanin A, a natural FAAH inhibitor, to endogenously increase dopamine levels by inhibiting the degradation of anandamide. It has exhibited various medicinal benefits, including anti-inflammatory, estrogen mimicking, and glucose lipid modulatory activity, in addition to cancer-preventives and neuroprotectant properties [46-55]. A variety of pharmaceuticals is available in transdermal patch form, and this delivery method can readily be appropriated to boost the bioavailability of nutraceuticals [57].

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