

ADHD and the Endocannabinoid System

Several physicians who recommend/approve medicinal cannabis as an important part of their medical practice have seen/noticed an increasing the number of patients coming in who have been diagnosed with Attention Deficit Disorder (ADD) or Attention Deficit with Hyperactivity Disorder (ADHD) or who they diagnose as ADD/ADHD.

What is meant by these diagnoses.

• What is ADHD?

These diagnoses don't correspond to any recognized pathology. For example, if we say somebody has appendicitis, we can look at the removed appendix under the microscope and see some specific changes like a lot of a certain type of cells that create an inflammatory response. Somebody with asthma will have certain easily identifiable changes in their lungs, etc. A person with ADD/ADHD does not have any such changes as far as we know. What ADD/ADHD have is a certain group of symptoms, like difficulty concentrating, hyperactivity, behavior issues, etc. also appears to be a deficiency in free dopamine.

The cause of ADHD is unknown, although scientists feel that at least 50% of cases have a genetic component. Also studies show that people with ADHD have 70% more dopamine transporters, thereby decreasing the availability of free dopamine.

Attention Deficit Hyperactivity Disorder (ADHD), was formerly called hyperkinesis or minimal brain dysfunction. It is described as a chronic, neurologically based syndrome characterized by any or all of three types of behavior: hyperactivity, distractibility, and impulsivity. Hyperactivity refers to feelings of restlessness, fidgeting, or inappropriate activity (running, wandering) when one is expected to be quiet; distractibility to heightened distraction by irrelevant sights and sounds or carelessness and inability to carry simple tasks to completion; and impulsivity to socially inappropriate speech (e.g., blurting out something without thinking) or striking out. Unlike similar behaviors caused by emotional problems or anxiety, ADHD does not fluctuate with emotional states. While the three typical behaviors occur in nearly everyone from time to time, in those with ADHD they are excessive, long-term, and pervasive and create difficulties in school, at home, or at work. ADHD is usually diagnosed before age seven. It is often accompanied by a learning disability. More recently there has also been described adult ADHD.

• Treatment

While we strongly suspect that there is an important role for dopamine dysfunction (probably to little but a few researchers say too much), we don't really know the specific cause of the ADD/ADHD symptoms, and there is no routine test for dopamine levels, so the diagnosis becomes what we call a "diagnosis of exclusion." That is, we make sure the person does not have some other identifiable condition, such as depression, learning

disabilities or a physical problem. If they don't, and have a certain number of symptoms from a predefined list, we label them with ADD/ADHD and give a drug that tends to make them a bit more manageable. The accepted drug treatments tell that Ritalin cures nothing but in many cases many make the patient more manageable.

Conventional ADD treatment usually includes behavioral therapy and emotional counseling combined with sympathomimetic medications (drugs that stimulate the sympathetic nervous system), such as methylphenidate hydrochloride (Ritalin) or dextroamphetamine (Dexedrine), Atomoxetine (Strattera), Amphetamine mixture (Adderal) or long-acting methylphenidate (e.g., Metadate LD, Concerta, Ritalin LA), that in many cases make the patient more manageable. They also have many unacceptable side effects.

Cannabis Safety

The first dictum of medicine is "first, do no harm." Another bedrock principal is that a prescriber must balance off the side effects of the treatment with the benefits. With ADD, the use of Ritalin and other stimulants has been routinely and repeatedly criticized because of their side effects profile. Not surprising all of my patients with ADD have been critical of either the side effects of these drugs, the lack of effectiveness or both. They have found cannabis to be both more effective and have far fewer side effects.

No less an authority than DEA Administrative Law Judge, Francis L. Young, in 1988, after a two-year hearing to reschedule cannabis said:

"Nearly all medicines have toxic, potentially lethal effects. But marijuana is not such a substance. There is no record in the extensive medical literature describing a proven, documented cannabis-induced fatality ... Simply stated, researchers have been unable to give animals enough marijuana to induce death .. In practical terms, marijuana cannot induce a lethal response as a result of drug-related toxicity ... In strict medical terms marijuana is far safer than many foods we commonly consume ... Marijuana, in its natural form, is one of the safest therapeutically active substances known to man."

When a medication gives you a symptom that you did not want, we call that symptom a "side effect." When it comes to treatment of ADHD for many, cannabinoids have far fewer and less annoying side effects than the stimulants that are often used to treat AD/HD and other conditions. The most common stimulants are methylphenidate (Ritalin, Concerta, Metadate-ER) and amphetamine (Dexedrine, Dexedrine Spansules, Adderall). Some individuals who take stimulants experience mild problems, some much more significant, unpleasant side effects. Some are simply unable to tolerate stimulants. Many people simply stop their prescribed stimulant medication instead of working with their physician to find a way to decrease side effects. Cannabinoids offer another viable option.

What is Association? What is Case and What is Self-Treatment?

A study reported in Clinician Reviews in 2000 entitled "Treating ADHD May Prevent Substance Abuse" found that:

"... untreated ADHD presents a significant risk factor for Substance Use Disorder (SUD) in adolescence, whereas treating ADHD may reduce this risk." (NOTE: I have no idea why substance use - as opposed to substance abuse- is a disorder.) At any rate, the authors "point to previous studies in which they found ADHD-SUD associations in adults with ADHD who had never been diagnosed or treated as children. Further examination is necessary in order to evaluate the risk factors for girls and nonwhite boys. However, these findings may reduce apprehension in treating children who have ADHD and promote earlier intervention. This, in turn, may prevent the academic, psychiatric, and interpersonal complications of ADHD in adolescents, and subsequently, in adults.

In some cases where Ritalin is ineffective or unacceptable, cannabis has been found to be helpful.

• Cannabis Studies

Much of the evidence about the medicinal use of cannabis is anecdotal, however that is changing. On 11/19/2000 Daniel Q. Haney of the Associated Press wrote:

"Maybe the smoke is about to clear in the debate over medical marijuana. Few ideas, it seems, are so firmly held by the public and so doubted by the medical profession as the healing powers of pot. But at last, researchers are tiptoeing into this field, hoping to prove once and for all whether marijuana really is good medicine.

"To believers, marijuana's benefits are already beyond discussion: Pot eases pain, settles the stomach, builds weight and steadies spastic muscles. "And that's hardly the beginning. They speak of relief from MS, glaucoma, itching, insomnia, arthritis, depression, childbirth, attention deficit disorder and ringing in the ears.

Marijuana is a powerful and needed medicine, they say, tragically withheld by misplaced phobia about drug addiction."

In his article, Haney points out that some are not impressed with these anecdotal reports stretching over centuries funding. However the State of California has founded the Center for Medicinal Cannabis Research, headquartered at UCSD has several million dollars to scientifically study cannabis' medical efficacy. There are 18 FDA-approved studies at UCI, UCSF, UC Davis, and UCSD School of Medicine. In Haney's words:

"Pot has many effects on the body, including some that are probably worthwhile. But does it substantially relieve human suffering, they ask? And if so, is it any better than medicines already in drugstores?"

"For the first time in at least two decades, marijuana the medicine is being put to the test. Scientists say they will try to hold marijuana to the same standard as any other drug, to settle whether its benefits match its mystique.

"One way to buff up a pharmaceuticals' raffish image -- especially one that's a drug in more than one sense of the word -- is to call it something else. When the University of California at San Diego started the country's first institute to study the medical uses of marijuana this year, they named it the Center for Medicinal Cannabis Research. Cannabis is the botanical term for pot.

"We talked about it a lot," says Dr. Igor Grant, the psychiatrist who heads the new center. "Marijuana is such a polarizing name. We don't want this institute to be caught in the crossfire between proponents and antagonists. Ultimately, if cannabis drugs become medicine, they will almost certainly be known by that name, not marijuana."

The Center for Medicinal Cannabis Research appears to be living up to its expectations. It was authorized to give out \$9 million to California researchers over the three years from 2000-2003. This has been enough funding to underwrite 18 NIDA/FDA-approved studies. At least one or two are looking at cannabis and ADHD.

Research Implications

Here's my take on the implication of the brain studies related to cannabinoids.

- **Cannabinoid Receptors**

There are two cannabinoid receptors in the body – CB₁ located in the brain, and CB₂ in the periphery. For CB₁ there are two natural ligands in the body anandamide (arachidonyl ethanolamide) and 2-AG (2 arachidonyl glyceride). For CB₂ receptors, palmitylethanolamide is the natural ligand.

- **Cannabis/Tetrahydrocannabinol**

There are over 400 different chemicals in marijuana, about 66 of which are known as cannabinoids. These chemicals are found nowhere else in nature. The most pharmacologically important cannabinoid in marijuana is known as delta-9-tetrahydrocannabinol (9 THC). It binds to CB₁ receptors (G-protein-coupled receptors) that are present on presynaptic membranes in several parts of the brain. THC is the main psychoactive (mind-altering) ingredient in marijuana. It is clear though that several other cannabinoids and possibly other chemical components of the plant have therapeutic value. These plant cannabinoids can stimulate the body's endocannabinoid system.

- Endocannabinoid System

Cannabinoid CB(1) receptors are highly localized in the central nervous system. A 2000 report of the work of Martin, Ledent, et.al. in the February 2002 issue of *Psychopharmacology* concluded that endogenous cannabinoids, through the activation of CB1 receptors, are implicated in the control of emotional behavior and participate in the physiological processes of learning and memory.

The highest concentration of CB1 THC receptors in the brain are found in the hippocampus (where memory is formed), cerebellum (deals with coordinating movements and balance), the striatum, amygdala (emotion), cerebral cortex (higher centers of reasoning) and the basal ganglia. An important class of neurons that express high levels of CB(1) receptors are GABAergic interneurons in the hippocampus, amygdala and cerebral cortex. They may act as retrograde synaptic mediators (inhibitors of neuronal transmission). This phenomena is caused by the depolarization-induced suppression of inhibition or excitation in hippocampus and cerebellum. In plain English, cannabinoids may help treat ADHD by decreasing both the amount and speed of sensory input to the midbrain and forebrain. The endocannabinoid system represents a mechanism by which neurons can communicate backwards across synapses to modulate/decrease their inputs. Increased free dopamine released by cannabinoids stimulates increased dopamine in the intasynaptic cleft. This anandamide stimulation can release dopamine and from the synaptic endplate. This can depolarize that nerve, making it harder to stimulate the nerves stops the brain from being inundated from both internal and external stimuli.

Cannabinoid receptors are co-localized with dopamine receptors suggesting that cannabinoids influence the dopaminergic processes. They probably can release dopamine which influences neurons to depolarize thereby making it harder to stimulate them. With fewer inputs to the higher centers of thinking and with the neural input being slower, it makes it that much easier for the patient to focus and process these thoughts.

- Cannabinoids

It is possible that, in part at least, cannabis' effects are due to the cannabinoids, a major nonpsychotropic constituent of cannabis. It was recently discovered that the cannabinoids (as opposed to THC) effect the inhibition of anandamide uptake.

- Prefrontal Cortex (PFC) and Midbrain

The prefrontal cortex (PFC) is essential for control of attention, organization and planning. Lesions to the PFC in humans can produce distractibility, hyperactivity, and impulsivity (Stuss, Eskes, & Foster, 1994). The PFC projects to many subcortical (e.g., lower down in the brain) regions, including the dorsal and ventral striatum, thalamus, amygdala, substantia nigra, and ventral tegmental area (Alexander, DeLong, & Strick, 1986) all areas with high concentration of THC receptors. The motor dysregulation characteristic of ADHD and neuroimaging data suggest that dysfunction in the striatum or

in the cortical regulation of striatum is involved in the pathophysiology of ADHD. This dysregulation may be associated with lower than normal levels of free dopamine.

- Dopamine

The power for the getting neural impulses around the brain are the neurotransmitters. Neurotransmitters cross the synapse and stimulate receptors in the next neuron causing transmission of nerve impulses. Neurotransmitters include norepinephrine, serotonin, acetylcholine, dopamine and anandamide (the naturally occurring cannabinoid).

Catecholamines include Dopamine, Norepinephrine, and Epinephrine (adrenalin). They control the so-called adrenergic systems. Some of these neurons radiate from the limbic system and discharge neurotransmitters in a diffuse manner into the frontal cortex, i.e. into broad areas of brain tissue as opposed to delivering the chemical to specific synapses. They thus account for "global vigilance" (staying awake), mood, fight or flight response, etc. Dopamine also contributes to the feelings of bliss and regulates feeling of pain in the body. Chocolate, coffee, nicotine, THC and stress all have been found to increase Dopamine. Thorazine and Haldol block Dopamine action (less learning, remembering and motivation).

Attention-Deficit Disorder (ADD) and Attention-Deficit Hyperactivity Disorder (ADHD) patients probably have less free synaptic dopamine available than the norm. They may produce less dopamine than those who do not have this condition. Also a preliminary study reveals that adults with ADD/ADHD have 70 percent more dopamine transporters in their brains than normal subjects. These transporters tie up dopamine leaving less free dopamine available for neuro stimulation.

- Low Dopamine

In 2000 Grace proposed a model of dopaminergic dysfunction in ADHD at the cellular level that explain many of the symptoms of ADHD. He suggests that, possibly because of reduced stimulation from PFC, children with ADHD have low tonic dopaminergic activity. Low tonic stimulation of inhibitory autoreceptors produces high phasic activity in the nucleus accumbens, and possibly other subcortical sites as well, that may result in dysregulated motor and impulse control,

Dopamine receptor oversensitivity. I must confess I do not know what that is, also may cause the body to decrease the amount of dopamine being produced. A shortage of dopamine in the frontal lobe can contribute to poor working memory.

- Stimulants May Inhibit Dopamine Breakdown

There is strong evidence that the catecholamines dopamine and norepinephrine are important in the pathophysiology of ADHD, as well in the mechanism of therapeutic action of stimulant drugs. Because of the known effects of exogenous stimulants in blocking reuptake of catecholamines and (in the case of d-amphetamine) facilitating their release, it has traditionally been believed that the stimulants compensate for catecholamine deficiency in ADHD.

Hyperactivity, and possibly poor motor impulse control, in ADHD results from dopaminergic dysfunction in the limbic system. Some believe the cause is excessive dopaminergic activity. In this theory, stimulation of the presynaptic autoreceptors reduces phasic dopamine release. The striatum and/or nucleus accumbens are possibilities for places in the limbic system so affected. Stimulant drugs may reduce hyperactivity by reducing activation of the striatum, possibly through a mechanism that involves stimulation of inhibitory pre-synaptic autoreceptors.

By blocking dopamine reuptake, stimulants increase levels of dopamine in the extracellular space, thus increasing the stimulation of impulse-regulating presynaptic autoreceptors. This acts as an inhibitor of subsequent stimulation of these neurons. The increase in intrasynaptic dopamine thereby reduces the ability to stimulate neurons in the limbic system. This then can decrease hyperactivity and increase focus.

- **Cannabinoids Regulate Neural Traffic**

There are essentially two kinds of brain cells, according to Stanford University neuroscientist Dan Madison. There are the principal cells that make up what he likened to a superhighway system of long-range information movement, and there are "interneurons," which are like traffic signals along that highway.

"Cannabinoids are a way for the principal cells to regulate the traffic lights," Madison said. After two years of laboratory study and frustrating dead ends, Wilson and Nicoll found that the role of the brain's cannabis is to make the feedback system work. Harvard researchers, working independently, found an essentially identical role for endogenous cannabinoids in another part of the brain, called the cerebellum, which helps to control motor function.

"It's a way for a nerve cell to adjust the gain or intensity of the information coming into it," Nicoll said. "It turns up the amplifier, in a way, and allows more input to get through." Conversely of course one can turn down the gain and decrease the input which gets through.

These adjustments seem to have an important role in the brain's uncanny ability to synchronize the firing of nerve cells scattered throughout the brain linking behavior with mood and memory with vision or hearing. Thousands of signals thus become molded into vast oscillations, helping the brain bind together different aspects of perception into coherent state of mind -- a feeling of being in love, perhaps, when we look at someone.

- **Retrograde Messenger System/Synaptic Inhibition**

Experiments in the last few years have shown that in any neural circuits where *endocannabinoids* are present these endocannabinoids *may participate in a retrograde messenger system whose goal is presynaptic inhibition*. Endocannabinoids serve as the messengers in this system, and CB1 serves as the receptor that initiates the inhibition. This is especially important in signaling between neurons in the hippocampus, where

strengthening and weakening of neural connections, thereby reorganizing neural circuits, is thought to be a cellular correlate of learning and memory.

Cannabis appears to treat ADD and ADHD by increasing the availability of dopamine. This then has the same effect but is a different mechanism of action than stimulants like Ritalin (methylphenidate) and dexedrine (1) amphetamine which act by binding to the dopamine and interfering with the metabolic breakdown of dopamine. Cannabis (THC) is an anandamide agonist, that is it stimulates the anandamide (CB1) receptor sites.

Researchers working on Tourette's Syndrome (TS) favorable response to Δ^9 -THC said: "neuroanatomical structures which are probably involved in TS pathology are heavily associated with the CB₁ receptor system. Considering an involvement of the dopamine system in TS pathophysiology it can be speculated that tic improvement might be caused by an interaction between cannabinoid and dopamine mechanisms. I believe that this is true for the rather closely related ADHD.

• **Research**

What does research say about cannabinoids controlling ADD or hyperactivity. An animal model study, published in the May 2000 issue of the Journal of Neuroscience, reports that synthetic compounds developed to block the way anandamide – the body's own cannabis-like compound or cannabinoid – is inactivated or broken down could correct forms of hyperactivity, such as attention deficit disorder.

Research by Dr. Daniel Piomelli at UCI also suggests a possible mechanism of action for cannabis in treating ADD. Dr. Piomelli, professor of pharmacology, led a team that found that a chemical called AM404 reversed the normal inactivation of a naturally occurring chemical in the brain called anandamide, which is related to marijuana's active ingredient and opposes or counteracts the actions of dopamine. According to Reuters article, Piomelli's study showed that: A chemical that boosts a marijuana-like substance in the brain may insure new treatments for brain disorders such as schizophrenia, Parkinson's disease, and attention-deficit/hyperactivity disorder (ADHD). (Note: Arachidonoyl ethanolamide (AEA) was the first endogenous cannabinoid to be isolated and characterized as an agonist acting on the same receptors (CB₁ and CB₂) as tetrahydrocannabinols (THC). This means that stimulating the anandamide receptors could effectively treat ADD.

Piomelli and his colleagues found that AM404 targeted nerves that produced unusually high levels of dopamine and caused exaggerated movements and other problems in rats. Instead of directly encouraging the production of dopamine-curbing anandamide, AM404 was found to discourage the disintegration of existing anandamide. More anandamide was then available to bind to receptors on nerve cells and reduce the stimulation of nerve cells by dopamine.

What I believe is happening is two things. One is that release of anandamide slows down the rate of neurotransmission. A second action from stimulating anandamide receptor

sites may be the stimulation Renshaw cells. Renshaw cells are in the midbrain and their neurons go downward in the brain. Their function is to turn off some of the cells which provide sensory input.

Piomelli's studies showed that by reversing the inactivation of anandamide, AM404 is able to gently curb the exaggerated movements and other disorders caused by too much dopamine activity in nerve cells. This position that too much dopamine is the problem is held by a minority of researchers in this field. Piomelli believes that in the case of Parkinson's disease, patients have too little dopamine, while people with ADHD, schizophrenia or Tourette's syndrome may have too much. His hope is that AM404 will lay the groundwork for a new class of drugs that either boost or block dopamine, without the side effects linked to current treatments.

Piomelli told Reuters Health in an interview. "Our results are interesting," he said, "because they show that you can modulate dopamine without acting on the dopamine system." Instead of directly encouraging the production of dopamine-curbing anandamide, AM404 was found to discourage the disintegration of existing anandamide. More anandamide was then available to bind to receptors on nerve cells and reduce the stimulation of nerve cells by dopamine.

Piomelli and his colleagues showed for the first time that in rats, anandamide naturally counters dopamine. Usually, though, anandamide is inactive in the brain. The California team's latest experiments in rats reveal that AM404 stops anandamide from being "drained from the brain," which allows it to suppress dopamine.

A UCI news release of May 1, 2000 states that:

"If further research proves successful, the chemical could be used to treat schizophrenia, Tourette's, Parkinson's, autism and attention-deficit disorder, all of which are currently treated by drugs that attack the dopamine system in the brain." Piomelli's research shows "you can modulate dopamine without acting on the dopamine system." These conditions are treated with drugs that affect the dopamine system. Piomelli points out that these existing treatments have side effects such as lethargy and impaired sexual activity. The potential for anandamide-boosting drugs to work against these disorders has some anecdotal backing. Anandamide's counterpart, marijuana, is used by many schizophrenics who report that it relieves their symptoms, Piomelli noted.

"But," he said, "we are not implying that marijuana is use for these conditions."

Piomelli is quoted by USA Today that, "Marijuana has a lot of pharmaceutical and pharmacological potential. The potential now is becoming very, very clear." Many decades-old prejudices are being lifted and that is reflected by the considerable funding that the federal government is giving to research marijuana.

Marijuana, according to Piomelli, is far less selective than anandamide in activating brain cells. Because pot smoking overstimulates the brain, he said, cells eventually become

desensitized to any benefits the drug initially brings. SOURCE: Journal of Neuroscience May 2000.

"I would be very surprised that if in the next 10 years there isn't an important new medicine developed from our better understanding of the cannabis system in the body," says Piomelli.

While Piomelli himself has discounted the use of cannabis for these disorders, this research clearly lays out a potential mechanism of action. An article by UCI staff writer Andreas Von Bubroff states that: "Anandamide is similar to marijuana's active ingredient, THC and belongs to a class of neurotransmitters called endogenous cannabinoids since it is naturally produced by some of the brain's nerve cells." It is known that cannabis is neuroprotective and in practice it has shown to provide relief for some epilepsy, Tourette's and some ADD sufferers. I myself have had several patients who have benefited from cannabis for ADD and with far fewer side effects than Ritalin.

Lastly, there is a six (6) page paper by Kurt E. Patterson discussing marijuana and ADD. In it he states that "There is some evidence available that medical marijuana has been found to be an effective medication for some types of ADD by other researchers in the field. (1) Unfortunately, ADD encompasses such a variety of conditions that the limited amount of research in the field leaves many of the effective therapeutic mechanisms under-investigated. Considering the regulatory difficulties in researching the effects of medical marijuana, it isn't surprising that the information regarding medical marijuana and ADD is largely anecdotal(2)."

• **What does Proposition 215 mean?**

It is difficult to parse the language where on the one hand the preamble talks about "serious illnesses" and on the other Proposition 215 gives a list of conditions including nausea, glaucoma, migraine, pain and then adds for "any other condition for which a physician feels that cannabis may be useful." An argument was made for a broad interpretation of 215 approvals and recommendations by no less authorities than the California DA's Association, California Sheriffs Association, and California Narcotics Officer's Association in their ballot argument against 215. They argued that if 215 passed, cannabis could be recommended for anything. A somewhat narrower reading is argued for by the brief of the CMA and concurred in by the 9th circuit court of appeals, arguing that 215 protects a physician's first amendment right to communication with his patient and the patient's right to hear what medications, be they prescription, herbal, vitamins or alternatives and complementing medicine may be helpful for their medical condition.

ADD has been termed a serious enough condition that hundreds of thousands of school children are treated with (some would say subjected to) the not so benign medication Ritalin. ADD as well as ADHD and adult ADD or ADHD have been shown to be very disruptive on people's lives – their self-esteem, their ability to succeed in life, their ability to do well in school. There are numerous websites on ADD and ADHD which assert that

this is a serious condition. ADD and ADHD then qualify under a reasonable interpretation of either a narrow or broad interpretation of 215.

Several physicians in California who regularly made 215 recommendation (Dr. Frank Lucido, Dr. Tom O'Connell, Dr. Tod Mikuriya) have indicated that they have made many recommendations for the medical use of cannabis to treat ADD. Dr. Lester Grinspoon, Emeritus Professor of Psychiatry at Harvard School of Medicine and author of Marijuana, The Forbidden Medicine, has a website which lists anecdotal reports of the medicinal benefits of cannabis. Out of a sample of 25 displayed anecdotes to his website 3, or 12% were describing cannabis' benefits for treatment of ADD. A March 5, 2002, a 48-Hours TV program chronicled the effectiveness of a medical recommendation for the treatment of ADD in an eight year old child. A California court determined that this constituted an appropriate treatment for this child. The book Jeffries Journey discusses this case.

There is overwhelming anecdotal evidence regarding the benefit in treating ADD and ADHD with cannabinoids but also that many view ADD as a serious condition. Further, it is clear that the FDA, at least in the person of Administrative Law Judge Francis Young, has found that marijuana is safer than Ritalin.