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CLINICAL APPLICATION OF BASIC RESEARCH: CANNABIS AND CANNABINOIDS IN THE TREATMENT OF ADD/ADHD

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Cannabis and cannabinoids effectively treat ADHD with fewer side effects than traditional sympathomimetic treatments (e.g., amphetamines, Ritalin®, Adderal, Strattera). With today's skyrocketing health costs, here is a treatment that does not require pharmacies and health insurance. This paper will discuss the experience of doctors in California in treating ADD/ADHD with cannabis and cannabinoids. It will look at the work of Alger, Pommier and others in discussing the role of retrograde inhibition and the endocannabinoid system in ADD/ADHD. More importantly, it will suggest how cannabis and cannabinoids affect dopamine and impacts retrograde inhibition. The presentation will discuss a practical clinical application of some of what scientists have learned the endocannabinoid system. It will address clinicians treating patients with cannabis, cannabinoids and the prospect for using metabolic anandamide blockers for treating ADHD.

ADHD is a costly problem that strains medical/mental health, educational, and legal institutions. ADHD affects 3-5% of Americans. It is one of the most common psychiatric disorders of childhood and in adults frequently results in tragic consequences in professional and personal lives. ADHD is characterized by persistent impairments in attention (or concentration) and/or symptoms of hyperactivity and impulsivity. The preponderance of studies show marijuana use is overwhelmingly prevalent with ADHD sufferers, either as a self-medicament or for recreation. While some apply preconceptions that marijuana exacerbates ADHD almost all California cannabinoignists believe cannabis and cannabinoids have substantially improved the lives of ADHD sufferers, and with less negative side effects than common stimulant drug ADHD treatments. As we have come to understand more about the brain and the role of dopamine and the endocannabinoid system, we are starting to unravel how cannabis, anandamide and the synthetic delta 9-thc-dranabinol, act to free up dopamine and decrease the overstimulation of the midbrain.

It turns out for many with ADD/ADHD cannabis or cannabinoids are a better choice than the traditional sympathomimetic drugs. For many years stimulants (sympathomimetic drugs) have been the mainstay for treating ADHD. They are thought to work by tying up dopamine transporter thus freeing up dopamine, previously bound to the dopamine transporter, thus having more free dopamine to engage in retrograde inhibition. Dopamine is essentially acting as a damper on neurotransmission by depolarizing the neuron that just released it. The stimulants main drawback is that they come with a host of unacceptable side effects-jitteriness, anxiety, sleep difficulty, appetite suppression and a propensity to be quick to anger.

It turns out that cannabis also frees up dopamine and it has a very benign side effect profile. Noting cannabis' vastly superior side effect profile DEA Administrative Law Judge, Francis L. Young, after a two-year hearing to reschedule cannabis in 1998 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.... 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."

Clinicians have found that the results in treating ADHD with cannabis can be quite impressive. Patients report grades going from Cs and Ds to As and Bs. One of my patients said "I graduated from the Maritime Academy because I smoked marijuana," and another "I got my Ph.D because of smoking marijuana." Almost universally ADHD patients who therapeutically used cannabis reported it helped them pay attention in lecture, focus their attention instead of thinking of several ideas almost at the same time, helped them to stay on task and do their homework.

9 Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder. NIH Consensus Statement Online 1998 Nov 16-18; 16(2): 1-37.
CANNABINOIDS CB1 RECEPTOR ANTAGONIST BLOCKADE AT BIRTH MAY BE ASSOCIATED WITH ADHD

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Attention Deficit Hyperactivity Disorder (ADHD) is a condition that becomes apparent in some children in the preschool and early school years, but also appears at adulthood. It is estimated that between 3-5 percent of children have ADHD in USA, and 5-10 percent in the Israel. ADHD is characterized by inattention, impulsivity and/or hyperactivity. A well-known feature of ADHD is the positive response to psychostimulants such as methylphenidate (Ritalin) and D-amphetamine (Adderall), expressed as a reduction in excess motor activity and improved concentration. Although ADHD has been known for over 80 years, the etiology and risk factors for ADHD are still unclear. Importantly, low birth weight may be one of the most important predictive factors of ADHD (Chadapim et al. 2005). Non organic failure-to-thrive (NOFTT) in infants is defined as an abnormally low weight and/or height for age without a known organic cause. In a series of studies performed in neonatal mice we have demonstrated that the cannabinoid CB1 receptor is critically important for feeding and weight gain, apparently caused by an oral-motor dysfunction, similarly to that which characterizes infants suffering from NOFTT (Fride et al., 2001; 2003; 2007). Children who suffered from NOFTT are thought to display behavioral and cognitive dysfunctions in later years. Here we propose that a deficient ECS (endocannabinoid system) at birth may comprise a risk factor for ADHD.

Methods: Male and female pups were administered a single injection of SR141617 (rimonabant, 5, 10 or 20 mg/kg), within 24 hours of birth. At two months of age, mice were tested in an assay for pre-pulse inhibition (PPI) of the acoustic startle response (ASR). At the age of 16 weeks the same mice were examined for motor activity in an open field, immobility ( catalepsy) on an elevated ring, for anxiety-like behavior in an 'elevated plus-maze' and in the Porsolt forced swimming test for depressive-like symptoms.

Results: Pups treated with 10 or 20 mg/kg rimonabant showed a reduction in body weight during the first 2 weeks of life. However as adults, all (surviving) mice were of normal weight. Behaviorally, both male and females displayed significant hyperactivity in the open field and on the 'ring'. We also observed a decreased performance in the PPI assay at both doses for the females but only at the 5 mg/kg dose for males. We observed a lower level of anxiety in the plus maze, again primarily in the males which had received 10 mg/kg SR141716. Compatible with this observation, a trend towards a reduced startle response was seen, again mainly in the males. In the forced swimming test, no differences were observed between rimonabant-treated and control mice. Preliminary observations suggest that DL-amphetamine administration (4 mg/kg) normalizes neonatal rimonabant-induced hyperactivity and PPI.

Conclusions: Our observations suggest that brief neonatal blockade of the cannabinoid CB1 receptor at birth precipitates symptoms of ADHD at adulthood as apparent in hyperactivity, impaired sensorimotor gating a tendency toward reduced 'anxiety' and the reversibility of these symptoms by amphetamine. In addition, similarly to observations in humans treated for ADHD (Pinkhardt et al., 2009), primary mood regulation was not affected in mice with blocked CB1 receptors at birth. We conclude that at least a subgroup of ADHD may be caused by a developmental deficiency of the endocannabinoid system.
MEDICINAL CANNABIS: HOW CANNABINOIDS CAN HELP TREATING ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD)?

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This work is a review of the Endocannabinoid System (ECS) implication in ADHD. It reports two European cases, sample of the growing number of Medicinal Cannabis (MC) recommended/prescribed for the treatment of ADHD cases.

Scientific studies have demonstrated a relation between cannabinoid receptors (CB1, CB2), endocannabinoids (Anandamide, 2-Arachidonylglycerol), the Central Nervous System and the Neuro-immune System. CB1 receptors, abundant in the brain, interact with the Dopaminergic System. Genetic studies found a correlation between Cannabinoids Receptors Gene and ADHD. Regarding behaviour, CB1 are possible targets to reduce hyper-impulsivity, Tourette Syndrome tics, fears, anxiety and improve emotional learning (synaptic plasticity) and distractibility. The neurochemical mechanism of action is Retrograde Signaling Inhibition. This is dopamine mediated. An increase in unbound cannabinoid levels leads to cannabinoids replacing dopamine bound to dopamine transporters binding sites. With more dopamine available to slow down the speed of neurotransmission there are fewer, slower moving neural inputs and the cerebral cortex has a better opportunity to focus and attend to the neural stimulation.

Cannabinoids are accepted by many cannabinoid medicine specialists for treating ADHD. Two patients, from Luxembourg (52, retired policeman) and France (35, engineer), had the opportunity to experiment MC therapy with Dutch products, available in pharmacies since 2005. Both report an improvement of their condition and chronic symptoms (distractibility, agitation, alcoholism, depression, anxiety, obsessive/suicide thoughts), without unacceptable side effects. CBD, no-psychoactive cannabidiol, was found necessary to reduce anxiety and adverse dronabinol effects (dronabinol/CBD ratio: 1/1-3/1). MC therapy was considered complementary to psychotherapy.

Both clinical experience, particularly in California, and scientific data suggest that targeting ECS with exocannabinoids is an exciting new alternative to treat ADHD. Many doctors, who have experience with patients, recommend cannabinoids for ADHD. Further clinical studies are required to investigate this new field.

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1. Patients Members of the International Association for Cannabis as Medicine (IACM)
4. The Neuropsychology of Impulsive Behaviour, T. Patti et. al., Trends in Pharmacological Sciences Vol.29 N°4 (Special issue : Pharmacology in The Netherlands) 192-199