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Cannabidiol as a suggested candidate for treatment of autism spectrum disorder

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ABSTRACT

Autism Spectrum Disorder (ASD) is characterized by persistent deficits in social communication, restricted and repetitive patterns of behavior, interests, or activities and often intellectual disabilities. ASD has a number of prevalent co-morbidities, such as sleep disorders, attention deficit/hyperactivity disorder and epilepsy. No effective treatment for the core symptoms of ASD is currently available. There is increasing interest in cannabinoids, especially cannabidiol (CBD), as monotherapy or add-on treatment for the core symptoms and co-morbidities of ASD. In this review we summarize the available pre-clinical and clinical data regarding the safety and effectiveness of medical cannabis, including CBD, in young ASD patients. Cannabidiol seems to be a candidate for the treatment of ASD. At present, however, there are no convincing pre-clinical or clinical data showing efficacy and safety of cannabinoid treatment in ASD patients.

1. Introduction

Autism spectrum disorder (ASD) defines a group of neurodevelopmental disorders that are frequently associated with general cognitive deficits (Zamberletti et al., 2017). DSM-5 criteria of ASD include:

A. Persistent deficits in social communication and social interaction across multiple contexts as expressed by deficits in social-emotional reciprocity, in nonverbal communicative behaviors used for social interaction or in developing, maintaining, and understanding relationships.
B. Restricted, repetitive patterns of behavior, interests, or activities including stereotyped or repetitive motor movements, insistence on sameness, inflexible adherence to routines or ritualized patterns of behavior, as well as hyper- or hyporeactivity to sensory input, or unusual interests in sensory aspects of the environment.
C. Symptoms must be present in the early developmental period.
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability or global developmental delay (American Psychiatric Association, 2013).

Worldwide prevalence of ASD is estimated to be approximately 1% (Lai et al., 2014). A recent study, however, demonstrated that by the age of 8 years one of 59 children in the USA meets the DSM-5-ASD criteria (American Psychiatric Association, 2013; Baio et al., 2018). ASD is more prevalent in males and is frequently accompanied by co-morbidities (Lai et al., 2014), the most common of which are sleep disorders (Garstang and Wallis, 2006) and attention deficit/hyperactivity disorder (ADHD) (Ghaziddin and Zafar, 2008). Other co-morbidities include psychosis, anxiety, mood and cognitive disorders.

Over the last decade, understanding of the genetic changes and the involvement of de-novo mutations in ASD is expanding (Ramaswami and Geschwind, 2018). Several dozen ASD susceptibility genes have been identified, collectively accounting for 10–20% of ASD cases (Geschwind, 2011). Involvement of epigenetic mechanisms and specific gene-environment interplay is also suspected, but more research is needed (Lai et al., 2014). Despite it being one of the most severe chronic childhood disorders with relatively high prevalence, morbidity and impact on the society, no effective treatment for the core symptoms of ASD is available yet. This may stem from the paucity of scientific data

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regarding the neurobiological basis of the disorder (Zamberletti et al., 2017). Most current interventions are behavioral and educational; pharmacotherapy (e.g. anti-psychotics, selective serotonin reuptake inhibitors (SSRIs) and stimulants) plays only a minor role (Lai et al., 2014), mainly in the treatment of irritability and aggressive behavior. Those are treated at present with the two FDA approved antipsychotics risperidone and aripiprazole (Stepanova et al., 2017). Unfortunately, these agents are not effective for the core symptoms of ASD.

Cannabidiol (CBD) is a non-psychotropic constituent of the cannabis plant (Chagas et al., 2014). More details on CBD and Δ9-Tetrahydrocannabinol (THC), are presented in Section 3 "Cannabinoids" below. The current review reports the available pre-clinical and clinical data regarding the potential effectiveness and safety of CBD in the behavioral symptoms and co-morbidities of ASD.

2. The endocannabinoid system in ASD

The endocannabinoid system (EC) consists of the endocannabinoids (Arachidonic Acid-derived compounds), endocannabinoid receptors and associated metabolic enzymes. The EC system acts as a neuromodulating network involved in the regulation of emotional responses, behavioral reactivity to context, and social interaction. The two main endocannabinoids are anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), both produced in the post-synaptic cell membrane as required. Binding of endocannabinoids to CB1 receptors modulates brain neurotransmission. Subsequently the endocannabinoids are metabolized by specific enzymes (Howlett et al., 2010; Zamberletti et al., 2017).

Endocannabinoid effect is due mainly to their binding to the cannabinoid receptors type 1 (CB1) and type 2 (CB2) (Zamberletti et al., 2017). CB1 receptors are G-protein coupled receptors (GPCRs) abundant in neurons, where they modulate neurotransmission. Outside the brain, CB1 receptors are localized in peripheral tissues, including hepatic, adipose, vascular, cardiac, reproductive and bone tissue. CB1 receptor signal transduction occurs through interaction with Gi/o-protein coupled receptors thereby inhibiting adenylyl cyclase, activating mitogen-activated protein kinases (MAPK), inhibiting voltage-gated $Ca2+$ channels, activating $K+$ currents (Kir), and influencing nitric oxide (NO) signaling (Howlett et al., 2010). CB2 receptors are located in the brain and in the periphery mainly in cells of the immune system (Rong et al., 2017). CB1 receptor stimulation is responsible for the cannabis psychoactivity, while activation of the CB2 receptor leads to attenuated inflammation, decreased tissue damage and accelerated regeneration in several disease states (Pacher and Mechoulam, 2011).

The EC system is often affected in ASD patients with comorbidities such as seizures, anxiety, cognitive impairments and sleep pattern disturbances (Zamberletti et al., 2017). A recent study showed lower plasma levels of the endocannabinoid anandamide in ASD patients as compared to healthy controls. This study suggests that impaired anandamide signaling may be involved in the pathophysiology of ASD (Karhson et al., 2018).

In another study an interaction between endocannabinoid signaling and oxytocin-mediated social reward was demonstrated. It was shown that oxytocin, a neuropeptide that reinforces parental and social bonding, drives anandamide mobilization in the mouse nucleus accumbens (NAc). This finding indicates that anandamide-mediated signaling at CB1 receptors, driven by oxytocin, modulates social reward. Thus, it seems that deficits in the signaling mechanism of anandamide may contribute to social impairment in ASD (Wei et al., 2015). It should be noted that some clinical trials suggest that intra-nasal administration of oxytocin may have therapeutic effects in ASD (Anagnostou et al., 2012; Tachibana et al., 2013).

3. Cannabinoids

Cannabis is one of the most widely used recreational drugs today. It derives from the genus of a flowering plant that includes three species: Sativa, Indica, and Ruderalis (Behere et al., 2017). A cannabis plant contains hundreds of different chemicals with about 60–80 ingredients known as cannabinoids (Brenneisen, 2007).

Cannabinoids are often divided into three sub-groups: phytocannabinoids, endocannabinoids and synthetic cannabinoids. Phytocannabinoids are the plant's naturally occurring cannabinoids and of those, CBD is the 2nd most abundant one (Gu, 2017).

The major cannabis psychoactive molecule is THC, which binds with high affinity to both the CB1 and CB2 receptor (Gallily et al., 2015). It induces euphoria, altered sensory perception and relaxation, also known as the "high" that is enjoyed by many users (Rong et al., 2017).

Another major constituent in cannabis is the above mentioned CBD which binds to the CB1/CB2 receptors with very low affinity and is devoid of psychotomimetic effects (Gallily et al., 2015). However, Russo claims that CBD seems to have psychopharmacological effects, since its administration is associated with some beneficial effects on anxiety and other conditions such as schizophrenia, addiction and possibly even depression. He suggested that "CBD should be preferably labeled as 'non-intoxicating', and lacking associated reinforcement, craving, compulsive use, etc." (Russo, 2011, 2017).

CBD displays a plethora of properties including anticonvulsive, sedative, hypnotic, antipsychotic, anti-inflammatory and neuroprotective ones. CBD also exhibits anti-oxidant effects, promotes neurogenesis (Cheng et al., 2014) and appears to be well tolerated by humans (Devinsky et al., 2014; Iuvone et al., 2004). Besides cannabinoid receptors, CBD also interacts with many non-endocannabinoid signaling systems (Gu, 2017). For example, CBD has been shown to be a potent agonist of the TRPV2 receptor (Transient Receptor Potential V2 receptor), also known as VRL-1 (Vanilloid Receptor Like 1), which may play a role in the regulation of oxytocin and vasopressin secretion (Khalil, 2012; Qin et al., 2008). CBD also inhibits the reuptake and enzymatic degradation of the endogenous cannabinoid anandamide, leading to an elevation in the anandamide levels (Bisogno et al., 2001), while THC does the opposite, namely decrease in the availability of anandamide (Rong et al., 2017). CBD also exerts agonistic activity at the 5-HT1a receptors, an effect that is hypothesized to mediate potential pharmacological antidepressant, anxiolytic and pro-cognitive effects (Linge et al., 2016; Russo et al., 2005).

The chronic use of marijuana has detrimental effects on cognitive function (e.g. executive function, learning, memory and attention). It has also been documented that chronic marijuana use can lead to amotivational syndrome and the induction of psychosis in populations at risk. These effects are mostly related to THC, while human interventional studies with CBD have showed no significant amplification of psychopathological measures. Furthermore, it was suggested that CBD has beneficial effects on several brain functions (Rong et al., 2017). Hence, the public interest in CBD therapy for several mental and neurological disorders is on the rise.

4. CBD use in medicine

The controversy regarding the benefits of medical cannabis and especially the use of the plant extracts in children is ongoing. In most countries worldwide cannabis, whether medicinal or not, is currently illegal. Still, the use of medical cannabis is growing, especially in countries such as Belgium, Canada, Australia, Netherlands and some US states (Behere et al., 2017).

Today, many commercial companies offer products consisting of medical cannabis extracts. These products differ in their administration mode (e.g. edible products, smokeable products, inhaled products, oil products for oral intake etc.) as well as in their cannabinoid extract content, as the content ratios of THC and CBD vary.

Several trials showed beneficial effects of medical cannabis use in different illnesses. For example, The National Academy of Sciences, Engineering and Medicine claims that there is substantial evidence for

the effectiveness of cannabis in the treatment of chronic pain in adults, as well as moderate evidence for improvement of short-term sleep disturbances in patients with chronic pain (Romero-Sandoval et al., 2018). Also, cannabinoids are currently used to reduce weight loss, emesis and pain that often accompany cancer. In addition, several cannabinoids have been shown to exert anti-proliferative and pro-apoptotic effects in various cancer types, both in vitro and in vivo (Massi et al., 2013).

In epilepsy, there is an increase in the demand to treat children and adults who suffer from treatment resistant seizures with medical cannabis. Surveys conducted among parents of children suffering from epilepsy suggest improvement following treatment with CBD-enriched cannabis extracts. These results however, do not necessarily apply when it comes to treating adults with epilepsy (Alexander et al., 2009). Still, in a retrospective study that examined the effect of CBD enriched medical cannabis oil on children with intractable epilepsy, the treatment caused a reduction in seizure frequency in 89% of patients (Tzadok et al., 2016).

Epilepsy is common (20–30%) in ASD and is more prevalent in individuals with autism-like behavior resulting from particular genetic predispositions (e.g. Angelman syndrome, Rett syndrome, Dup15q syndrome, etc.)(Gu, 2017). In a pre-clinical study that tested the efficacy of CBD in a mouse model for Dravet Syndrome, a severe childhood epilepsy disorder, CBD effectively reduced both seizures and autism-like behaviors (Kaplan et al., 2017b). In a clinical trial among patients who suffer from Dravet syndrome, cannabidiol treatment resulted in a greater reduction in convulsive-seizure frequency than placebo, but was associated with higher rates of adverse events (Nabbout et al., 2017). In a clinical study on Sturge-Weber Syndrome patients, chronic treatment of CBD decreased seizures significantly and improved quality of life (Kaplan et al., 2017a). In an online survey, parents of children with infantile spasms (IS) and Lennox-Gastaut syndrome (LGS) reported a reduction in seizures frequency in 85% of the cases, while 14% reported complete seizure cessation after administration of CBD-enriched cannabis preparations (Hussain et al., 2015). The U.S. Food and Drug Administration (FDA) recently approved Epidiolex, a CBD based oral solution, for the treatment of seizures associated with the two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older ("FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy, 2018").

5. CBD use in psychiatry

5.1. CBD and psychosis

In some cases, psychosis can be a comorbidity of ASD, with simultaneous onset of schizophrenia at adolescence or early adulthood (Sagar et al., 2013). The relatively high comorbidity rate of schizophrenia in ASD could be related to shared neurobiology, but also to arbitrary restrictions imposed by current diagnostic systems (Raja and Azzoni, 2010).

In children with ASD, fears, exaggerated anxiety reactions and thought process disorders may increase the risk of psychosis (Kyriakopoulos et al., 2015). However, assessment of psychiatric disorders in people with ASD is challenging, as negative symptoms and functional decline may overshadow positive psychotic symptoms in these people (Kildahl et al., 2017).

In patients with schizophrenia, adding CBD to ongoing antipsychotic treatment resulted in greater antipsychotic activity and beneficial effects, as compared to placebo add-on (Mcguire et al., 2018). A previous study however, that investigated the influence of CBD as a monotherapy in treatment-resistant schizophrenia found that it was ineffective (Zuardi et al., 2006). As for other types of psychosis, CBD showed a significant effect in decreasing Parkinson-related psychosis in Parkinson's disease patients with no significant adverse effects (Zuardi et al., 2009).

5.2. CBD and anxiety

Many ASD patients suffer from anxiety disorders that harm their quality of life (Gu, 2017; Haan et al., 2008; Perrin, 2011). CBD may possess anxiolytic effects both in animals and humans (Bergamaschi et al., 2011). In a sub-chronic pre-clinical study in a mouse model of post-traumatic stress disorder (PTSD), CBD administered daily one hour after predator stress reduced the long-lasting anxiogenic effects of chronic predator stress, partially via 5-HT1A receptor activation (Blessing et al., 2015; Campos et al., 2012). When tested in humans, CBD showed an anxiolytic effect in patients that suffer from social anxiety disorder (SAD), contrary to THC that may induce anxiety (Devinsky et al., 2014). In another study addressing this issue, CBD administered as pretreatment to patients with SAD significantly reduced anxiety, cognitive impairment and discomfort in a simulated public speaking test (SPST), and significantly decreased alertness in their anticipatory speech (Bergamaschi et al., 2011). According to a recent study, this positive effect of CBD on the anxiety level of SAD patients is related to its effects on activity at the limbic and paralimbic brain areas (Crippa et al., 2011).

5.3. CBD and addictive behavior

Research regarding ASD and addictive behavior is rather sparse. Since patients with ASD tend to exhibit low interest in exploring novel behaviors, the likelihood of them developing substance use disorders is fairly low. However, due to dysregulation of the dopamine reward system these individuals are more likely to develop addictive disorders and stimulatory behaviors such as increased interest in video gaming and watching television (Lalanne et al., 2017). Some studies indicate a correlation between Internet use addiction and autistic behaviors, which is in accordance with that speculation (Chen et al., 2015; Romano et al., 2014).

Nevertheless, in pre-clinical and early clinical trials it was shown that CBD has a positive effect on addictive behavior (Devinsky et al., 2014).

5.4. CBD, mood and cognitive disorders

It was previously shown that a variety of psychiatric co-morbidities may occur in ASD patients, the most common one being mood disorders (Ghaziddin and Zafar, 2008). As previously mentioned, THC use may be associated with onset or aggravation of depression, bipolar disorder, mania and psychosis (Rong et al., 2017). On the other hand, CBD possesses agonistic activity at the 5-HT1A serotonin receptor and shares similar mechanisms with lithium. These pharmacological properties may indicate its potential role in the treatment of mood disorders (Rong et al., 2017). In addition, a pre-clinical study using the tail suspension test (TST) in non-stressed Swiss mice, showed that CBD has properties common to classic antidepressants (Pupin et al., 2016).

Therapeutic CBD properties were investigated for cognitive deficits as well. In a pre-clinical study that tested the effect of CBD on cognition in an Alzheimer's Disease mouse model (APPxPS1), chronic CBD treatment reversed the cognitive deficits without affecting anxiety-related behaviors (Cheng et al., 2014).

In contrast to CBD in human patients, THC administration may result in memory impairment (Ranganathan and Souza, 2006; Rong et al., 2017). It was suggested that CBD may attenuate the anti-cognitive effects of THC (Rong et al., 2017), however, more studies are needed to substantiate this suggestion.

5.5. CBD and sleep disorders

Sleep disorders are highly prevalent among children with ASD.

Common sleep problems include difficulties in settling at bedtime with delays in sleep onset (sleep latency) once settled, short sleep duration and frequent and prolonged night waking (Garstang and Wallis, 2006). In the general population insomnia is the most common sleep complaint, and treatment with medical cannabis may be effective, especially when the insomnia is associated with pain (Gates et al., 2014). It has been claimed that long term use of cannabis may induce sleep disturbances (Gates et al., 2014). however, a case series indicated that CBD treatment may actually improve the quality of sleep in Parkinson's disease (Chagas et al., 2014).

5.6. CBD and ADHD

ADHD is one of the most common psychiatric co-morbidities in young ASD patients (Ghaziddin and Zafar, 2008), with comorbidity rates in the range of 40–70% (Antshel et al., 2016).

The DSM-5 criteria for ADHD diagnosis are: A) A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development; B) Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years; C) Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities); D) There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning (American Psychiatric Association, 2013).

In the general population, ADHD is a common disorder which affects mostly young patients (5%), but also persists into adulthood (3%) (Aguiar et al., 2010; Young et al., 2015). The disorder is characterized by inattention, hyperactivity and impulsivity (Cooper et al., 2017). Children diagnosed with ADHD are at increased risk for substance use disorders (Rasmussen et al., 2016).

In a pilot randomized placebo-controlled experimental study of a cannabinoid medication (an oral spray containing 1:1 ratio of THC:CBD) in adults who suffer from ADHD, there was no significant improvement in the cognitive performance, but there was a significant improvement in the hyperactivity, impulsivity and inhibition measures after the treatment with the medical cannabis (Cooper et al., 2017).

5.7. CBD and aggressiveness

Aggression and self-injurious behavior (SIB) may be associated symptoms of ASD and can result in significant harm to the patients, but also great distress for their families. The precise nature of the relationship between aggression or SIB and ASD remains unclear. These symptoms are therefore treated with a broad range of pharmacological approaches (Parikh et al., 2008). In two unrelated pre-clinical studies that examined the impact of CBD and THC treatments on aggressive behavior it was demonstrated that THC may attenuate aggressive behavior in rodents, while CBD does not (Ham and De Jong, 1975; van Ree et al., 1984).

5.8. The role of the endocannabinoid system in social behavior

As mentioned earlier, impaired social functioning is one of the major symptoms of ASD (Karhson et al., 2018), and the endocannabinoid system has a role in maintaining adequate social functioning (Karhson et al., 2016).

Several pre-clinical studies show that some agents who activate the endocannabinoid system may interfere with social behavior in animals. In one of these studies, chronic treatment of WIN 55,212-2 (a cannabinoid receptor agonist) in pubertal rats harmed their social behavior (Schneider et al., 2008). THC administration may lead as well to a reduction in social interaction in rats, while co-administration of CBD seems to attenuate this effect (Malone et al., 2009).

On the other hand, in a study that tested the influence of marijuana smoking on healthy human volunteers, subjects reported retrospectively that while smoking marijuana they were happier, friendlier and calmer, responded more warmly to others, seemed to have a better understanding of their peers' state of mind and were less likely to respond angrily or defensively. However, they had a harder time focusing and paying attention to what others said (Galanter et al., 1974).

A pre-clinical study in adolescent rats tried to resolve this inconsistency. The investigation showed that activation of the endocannabinoid system via the CB1 receptor, using the direct CB1 cannabinoid receptor agonist WIN55,212-2, reduced social play. However, stimulation of opioid and dopamine receptors by the indirect cannabinoid agonist URB597, which inhibits the hydrolysis of the endocannabinoid anandamide, enhanced social play. These results suggest that, depending on the pathway of the endocannabinoid stimulation, cannabinoid neurotransmission can both enhance and inhibit social interaction, at least in adolescent rats, (Trezza and Vanderschuren, 2008).

When it comes to cannabidiol, recent studies suggest that CBD has a positive influence on social behavior, and may therefore be considered an optional pharmacological treatment for ASD. As mentioned earlier, CBD treatment in a mouse model for Dravet Syndrome effectively reduced seizures and autism-like behaviors (Kaplan et al., 2017b). Furthermore, in an MK-801 rat model of schizophrenia, cannabidiol had no effect on MK-801-induced disruption of prepulse inhibition (PPI) or of hyperactivity, but showed a possible ability to inhibit MK-801-induced social withdrawal (Gururajan et al., 2011). In another study using a rat model for schizophrenia, chronic CBD administration attenuated the deficits in social interaction and cognition induced by prenatal poly I:C infection (Osborne et al., 2017). In a different study using SHR (spontaneously hypertensive rats) and Wistar rats, the lowest dose of CBD (1 mg/kg) increased passive and total social interaction of Wistar rats. However, the hyperlocomotion and the deficit in social interaction displayed by SHRs could not be improved by CBD regardless of the dosage size (Almeida et al., 2013).

6. CBD, neurodevelopment, mental disorders and ASD

The administration of cannabinoids for children and adolescents suffering from ASD is a controversial legal and ethical issue (Khalil, 2012). Those who oppose the use of medical cannabis in pediatrics claim that this treatment might harm young children and adolescents' brain development. Indeed, several pre-clinical and clinical studies that investigated the effects of cannabinoid consumption on brain development reported such harmful effects (Dow-Edwards, 2018; Rubino et al., 2016).

Brain development starts in-utero during early gestation and extends into late adolescence. Several important processes take place during neurodevelopment, including cell migration and differentiation and other cellular and anatomical changes. Childhood and adolescence are important periods for brain maturation and rearrangement, since processes like myelination, synaptic pruning and dendritic plasticity take place during that period. Maturation of some neurotransmitter systems (including the glutamatergic and the dopaminergic) and the endocannabinoid system occur during childhood and adolescence as well (De Bellis et al., 2001; Chambers et al., 2003; Schneider et al., 2008; Spear, 2000). Impact of cannabinoids on these systems may be relevant to the pathophysiology and pharmacotherapy of ASD.

Numerous human studies, including prospective longitudinal studies, demonstrate that early cannabis use is associated with major depressive disorder and drug addiction. A strong association between schizophrenia and cannabis use is also apparent, especially when considering genetic factors that interact with this environmental exposure (Chadwick et al., 2013). In a pre-clinical study in rats, chronic treatment with the synthetic cannabinoid full receptor agonist WIN 55,212-2 during pubertal development caused long-lasting behavioral disturbances in adulthood (Schneider et al., 2008; Schneider and Koch,

2003, 2005, 2007).

Interestingly, CBD appears to have neuroprotective effects that are relevant to addiction, cognition, and negative affect (Chadwick et al., 2013). It was also shown that CBD has very low toxicity in humans and other species, and no teratogenic or mutagenic effects induced by CBD were documented (Scuderi et al., 2009). However, some studies suggest that cannabis products might be contaminated with harmful agents (e.g., microbes, pesticides and heavy metals) and hence can cause potential damage to the user (Dryburgh et al., 2018). Another study in rats indicates that CBD has a potentially harmful effect on the male reproductive system (Carvalho et al., 2018).

In the field of pediatric mental illnesses, CBD is sometimes used as treatment for anxiety disorders. In a case report describing a 10 year old girl who suffered from PTSD after being sexually abused, it was reported that CBD treatment reduced her anxiety and improved her sleep (Shannon, 2016).

A double-blind randomized placebo-controlled trial designed to assess the safety, tolerability and efficacy of cannabinoid mix (CBD:THC in a 20:1 ratio) for behavioral problems in children and youth with ASD, is currently in phase two testing (NCT02956226). The trial takes place in Shaare - Zedek Medical Center in Jerusalem and is conducted by Drs. Adi Aran and Varda Gross as principal investigators. The trial's estimated completion date is January 2019, and it is hoped that it will provide stronger, more solid conclusions regarding cannabinoids treatment as a therapeutic option in children and young adults who suffer from ASD.

It is of note that two other clinical studies are currently conducted in ASD patients, one led by Dr. Grainne McAlonan from King's College in London, comparing cannabidivarin (CBDV) to CBD (NCT03202303) and one led Prof. Eric Hollander from Montefiore Medical Center/ Albert Einstein College of Medicine at NYC, using only CBDV (NCT03537950).

7. Conclusions

The use of cannabinoids in general and CBD in particular in the treatment of numerous medical and mental conditions, including ASD, is growing rapidly. In this review article we attempted to summarize the findings of pre-clinical and clinical studies regarding the involvement of the endocannabinoid system in physical and mental disorders and in neurodevelopment, as well as the safety and efficacy of CBD treatment in autistic behaviors and common co-morbidities of ASD. Unfortunately, no preclinical studies have thus far investigated the effects of any cannabinoid in validated animal models of ASD-like behaviors. There certainly is a big gap in the field and such studies are needed before drawing any conclusions on the potential therapeutic applications of cannabinoids in ASD. All current evidence is indirect and based on the efficacy of CBD in pathological conditions that could be also present in ASD. Hence, the potential efficacy of CBD in the context of ASD is only suggested.

Social interaction deficits are part of the core phenotypes of ASD while CBD has demonstrated some pro-social properties in pre-clinical studies. In addition, in some of the most common co-morbidities of ASD such as sleep disorder, ADHD, anxiety and seizures CBD may be effective as a monotherapy or additional treatment. In other ASD co-morbidities such as psychosis, addictive behavior, mood or cognitive disorders and aggressiveness the level of evidence is low.

Despite the lack of convincing clinical data on the effectiveness of cannabinoids in the treatment of ASD, treatment with cannabinoids seems to be relatively safe in adults and children. However, harmful effects of cannabinoids have been reported, some of them due to contaminated products that were not under regulatory supervision. Further pre-clinical and clinical studies are needed in order to examine the pros and cons of CBD and other cannabinoids in ASD, before they are established as treatment for ASD symptoms and co-morbidities.

Future randomized, placebo-controlled clinical trials, should evaluate the short- and long-term effectiveness of CBD and other cannabinoids (e.g. CBDV), in the treatment of the core symptoms of ASD (i.e. deficits in communication and social interaction, restricted-repetitive patterns of behavior) as well as the associated emotional and behavioral symptoms (i.e. irritability, anxiety, mood dysregulation, inattention, hyperactivity, aggressiveness and sleep impairment).

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