ARTIGO DE REVISÃO

CANNABINOIDS AS A TREATMENT APPROACH FOR ASD: A LITERATURE REVIEW

Canabinóides como linha de tratamento para o TEA, uma revisão de literatura

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ABSTRACT

Abstract: Given the increasing incidence and high economic and social costs associated with ASD, along with the need for effective pharmacotherapies for its core symptoms, alternative treatment options have become widely researched. The present study is a literature review that explored the DeCS/MeSH descriptors 'cannabinoid,' 'treatment,' and 'autism.' It is estimated that up to 80% of children with ASD experience sleep disturbances, such as prolonged latency for sleep onset, along with nocturnal and early morning awakenings, which are widely associated with alterations in the sleep-wake circadian cycle. In this context, it is known that the endocannabinoid system (eCB) is one of the main regulators of the sleep-wake cycle. However, the effect of phytocannabinoids on the sleep quality of children with ASD still lacks further clarification. Furthermore, these cannabinoids exhibit anti-inflammatory properties, reducing levels of pro-inflammatory cytokines and contributing to a neuroprotective microglial phenotype. In ASD, cannabinoid derivatives have demonstrated efficacy in controlling behavior and irritability. However, as of now, there is no FDA-approved product for regular use.

Keywords: Cannabinoids, Autism, Pharmacotherapy, Neuroprotection, Treatment, Behavior

RESUMO

Dada a crescente incidência e os altos custos econômicos e sociais associados ao TEA, juntamente com a necessidade de terapias farmacológicas eficazes para seus sintomas principais, as opções de tratamento alternativas têm sido amplamente pesquisadas. O presente estudo é uma revisão da literatura que explorou os descritores DeCS/MeSH 'canabinóide', 'tratamento' e 'autismo'. Estima-se que até 80% das crianças com TEA apresentam distúrbios do sono, como latência prolongada para o início do sono, juntamente com despertares noturnos e matinais precoces, que estão amplamente associados a alterações no ciclo circadiano sono-vigília. Neste contexto, sabe-se que o sistema endocanabinóide (eCB) é um dos principais reguladores do ciclo sono-vigília. No entanto, o efeito dos fitocanabinóides na qualidade do sono de crianças com TEA ainda carece de maior esclarecimento. Além disso, esses canabinóides exibem propriedades anti-inflamatórias, reduzindo os níveis de citocinas pró-inflamatórias e contribuindo para um fenótipo microglial neuroprotetor. No TEA, os derivados canabinóides demonstraram eficácia no controle do comportamento e da irritabilidade. No entanto, até o momento, não há nenhum produto aprovado pela FDA para uso regular.

Palavras-chave: Canabinóides, Autismo, Farmacoterapia, Neuroproteção, Tratamento, Comportamento

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INTRODUCTION

The Autism Spectrum Disorder (ASD) is characterized by an early neurobehavioral psychiatric condition marked by impaired social interaction, deficits in communication, and stereotyped, restrictive, and repetitive behavioral patterns, although it may present varied phenotypes [1]. It is estimated that ASD may reduce life expectancy by up to 20 years [2], and about 70% of patients are also affected by other conditions such as epilepsy [3], psychosis, anxiety, and mood disorders, which can delay diagnosis [4].

Several studies have demonstrated a strong genetic association with ASD, observing that monozygotic twins are much more frequently co-heritors of this syndrome than dizygotic twins [5-7]. In recent years, various genes, such as DLGAP2, and epigenetic mechanisms, such as DNA methylation, histone modification, and non-coding RNA, have been identified in relation to susceptibility to ASD [8]. A study analyzing the epigenomic activity of prolonged CBD exposure found that it promotes DNA methylation changes in hippocampal cells of adult mice at 3323 differentially methylated loci [9]. Additionally, ASD is also influenced by environmental factors associated with oxidative stress, neuroinflammation, mitochondrial dysfunction, and biochemical disorders such as toxins and neonatal infections [10].

Given the increasing incidence and the high economic and social costs related to ASD, along with the need for effective pharmacotherapies for the primary symptoms of this condition, alternative treatment options have been widely researched. In this context, there is a growing interest in the study of cannabis and its main non-intoxicating component, cannabidiol (CBD), the second most abundant phytocannabinoid in the Cannabis sativa plant [11]. CBD has been the focus of research for the diverse symptomatology of ASD, as this compound has therapeutic effects in some neurological conditions associated with this disorder, such as epilepsy [12] and anxiety in social phobia [13]. Moreover, recent studies have shown lower levels of circulating endocannabinoids, such as anandamide (AEA), in children with ASD [14], and another recent study demonstrated that CBD reduced the frequency of behavioral outbursts in children with ASD [15].

In the 1990s, cannabinoid type 1 (CB1R) and type 2 (CB2R) receptors were discovered, contributing to the understanding of the effects of cannabis components such as delta-9-tetrahydrocannabinol (THC) and CBD [16]. Both are G protein-coupled metabotropic receptors, and their expression varies according to body regions [17]. CB1R is found in the basal ganglia, cerebral cortex, hippocampus, and cerebellum, thus being related to motor control, cognitive functions, learning and memory, and is also present in sympathetic nerve terminals, lungs, reproductive system, and gastrointestinal tract. CB2R, on the other hand, is predominantly found in the spleen, tonsils, and thymus, in

peripheral cells of the immune system, with lower proportions in the pancreas, liver, bone marrow, skin, and bones [18]. In the brain, unlike CB1R, CB2R is found in low quantities, although its expression increases in microglia and other glial cells during inflammatory states [19].

THC is a CB1R agonist in the brain, potentially leading to anxiety and psychosis, while CBD is an allosteric modulator of CB1R and can act by reducing the agonistic effects of THC, besides being non-psychoactive and having a high toxicity threshold [20]. These two compounds also antagonize each other, especially at younger ages, regarding addiction, cognitive decline, and motivational loss, risks that are increased with THC use and reduced with CBD consumption [21]. Epidiolex, approved by the Food and Drug Administration (FDA) in 2018 for the treatment of two severe forms of epilepsy, Dravet syndrome and Lennox-Gastaut syndrome, and also approved for tuberous sclerosis, is a pure oral extract of CBD [22]. This approval may have been crucial for ASD patients, as 10 to 30% of these patients also have epilepsy, and various pathophysiological pathways are common to both disorders [23].

CBD can act in different regions of the Central Nervous System (CNS), many of which are also associated with the neurobiology of ASD, such as the hippocampus, cerebral cortex, lateral caudate-putamen, substantia nigra, amygdala, cerebellum, and globus pallidus, but especially in the basal ganglia and prefrontal cortex. CBD influences excitatory and inhibitory pathways in these regions by regulating glutamate and gamma-aminobutyric acid (GABA) levels, facilitating neurotransmission of both through agonism on the transient receptor potential vanilloid type 1 (TRPV1) receptor. Additionally, CBD, through antagonism on the G protein-coupled receptor 55 (GPR55), can increase GABAergic transmission, mainly in the basal ganglia. On the other hand, it is believed that CBD acts as an agonist on 5-HT1A receptors in the prefrontal cortex (PFC), suppressing glutamate and GABA transmission [24].

Given the current scenario of the lack of effective medications for the central symptoms of ASD, which bring significant impairments to the lives of patients and their families, and the emergence of different studies indicating a significant potential of cannabinoids in developing new therapies for this condition, the importance of research related to this theme becomes clear. In this context, our work proves its relevance as it seeks to discuss and delve deeply into different elements justifying the promising interest in cannabinoids as a line of treatment for ASD, based on the latest medical literature studies.

METHODS:

The present study is a literature review that utilized the DeCS/MeSH descriptors "cannabinoid" and "treatment" and "autism,"

combined with the boolean operator "AND," for the search in the PubMed, ScienceDirect, and BVS databases. The search period covered from 2019 to 2023. In this manner, 89 articles were identified according to inclusion criteria, including language in English, Portuguese, or Spanish, full-text availability, and relevance to the guiding question, such as a direct approach to the use of cannabinoids as a treatment for Autism Spectrum Disorder (ASD), therapeutic use of drugs, and the associated pathophysiology of ASD. In the end, all 89 articles were analyzed, and 16 were selected to be included in the present review.

RESULTS:

One of the studies included in our review concluded that a higher placebo response in children with Autism Spectrum Disorder (ASD) is primarily influenced by the child's understanding of the treatment and is also influenced by the relative worsening of symptoms compared to the average condition in the two years before the treatment initiation. The same study also reported finding no association between parental expectations about the treatment and the degree of placebo response, contrary to the researchers' suggestions in previous reports. This discrepancy may be attributed to the retrospective nature of the study, and thus, parents' responses to the Checklist of Experiences and Expectations may not have reflected their real-time expectations at the beginning of the study [25]. These results align with other studies that have also demonstrated high placebo responses in cannabinoid treatment research [26]. In line with the presented results, a meta-analysis comprising 22 studies involving children and adults with genetically determined intellectual disabilities showed a higher placebo response in individuals with higher IQ [27]. Moreover, the higher placebo response in the context of relative symptom worsening may be associated with an expected regression of symptoms to the previously established mean upon treatment initiation [28].

Another significant study included in our review conducted the first systematic review focusing on the inclusion of all studies investigating the role of the endocannabinoid system (eCB) in the interrelation between ASD and schizophrenia spectrum disorders [29]. Some points brought up by the studies included in this systematic review deserve further emphasis in our review. The effects of cannabinoid-based treatment appear to be dependent on epigenetic mechanisms, such as DNA methylation alteration in hippocampal cells, through genes determining neural functions common to both ASD and schizophrenia [30]. This was supported by other studies reporting common genetic vulnerabilities to ASD, schizophrenia, and cannabinoid use [31]. Exposure to THC predisposes genes related to ASD to inherent vulnerabilities to possible subsequent epigenetic disturbances [32]. Additionally, evidence has been established that

neuronal exposure to THC, whether acute or chronic, affects certain genes, causing synaptic, mitochondrial, and glutamatergic hypofunctional changes capable of impairing the proper activation of these cells, resulting in a negative impact on shared molecular pathways in neuropsychiatric disorders such as ASD, schizophrenia, and intellectual disability [33].

All these findings support the notion that THC/cannabis exposure can give rise to an intergenerational inheritance of altered DNA methylation patterns in genes related to ASD, such as DLGAP2, associated with brain areas relevant to schizophrenia later in life, such as the nucleus accumbens [34].

It is estimated that up to 80% of children with ASD experience sleep disturbances, such as prolonged latency for sleep onset, night awakenings, and early morning awakenings [35], which are widely associated with alterations in the sleep-wake circadian cycle [36]. In this context, it is known that the eCB is one of the main regulators of the sleep-wake cycle [37]; however, the effect of phytocannabinoids on the sleep quality of children with ASD still needs further elucidation.

In one of the studies included in this review, it was discovered that an improvement in the sleep quality of children with ASD can lead to improvements in both the central symptoms of this disorder and disruptive behaviors. However, treatment with CBD-rich formulations, whole-plant extracts, and pure cannabinoids did not bring more benefits regarding sleep disturbances compared to the placebo [38]. This finding aligns with the high placebo responses found in other cannabinoid treatment research studies [39], as mentioned earlier. This result also corroborates the negative acute effect of CBD on the sleep-wake cycle in healthy adults determined by another recent study [40].

DISCUSSION:

Among our discussion focuses is the comparison of response levels and tolerability observed in patients with Autism Spectrum Disorder (ASD) following the administration of whole-plant Cannabis sativa extract, purified cannabinoids, and placebo. Additionally, we explore the relationship between the neurobiology of cannabinoid action on their receptors, the cerebral distribution of these receptors, and the neural pathways involved in the etiology of ASD. The importance of a child's understanding of cannabinoid treatment in their placebo response, the correlation between the endocannabinoid system (eCB), schizophrenia, and ASD, as well as the frequent presence of sleep disorders in ASD patients are also points of discussion in our work.

Recently, a placebo-controlled study demonstrated that cannabinoid therapy has the potential to reduce the number of episodes of disruptive behaviors associated with ASD while maintaining high tolerability, especially for overweight ASD patients, as cannabinoid

treatment was associated with a net weight loss [41]. This finding is significant as it contradicts the obesity and metabolic syndrome generated by medications like risperidone and aripiprazole, both FDA-approved for treating comorbid irritability [42]. Another relevant issue addressed by the mentioned study [43] is that no significant advantages of whole-plant extract use over purified cannabinoids were observed, contrasting with the idea of the "entourage effect," where terpenes, flavonoids, and minor cannabinoids exert additive and synergistic therapeutic effects [44].

An important limitation in analyzing the therapeutic potential of CBD in different contexts is that many CBD formulations also contain other phytochemicals, such as THC, creating a confounding factor about which component is truly responsible for the positive results. In light of this, a comprehensive literature review [45] critically analyzed the results of clinical studies using only purified CBD products. One study included in this review used functional magnetic resonance imaging (fMRI) to compare the brain's response to purified CBD in individuals with and without ASD in a resting state, free of tasks, eliminating the limitation present in many studies that evaluate the drug's effect only on brain regions relevant to the proposed task [46]. This study found that CBD significantly increased the fractional amplitude of low-frequency fluctuations (FALFF) in the cerebellar vermis and the right fusiform gyrus. However, this effect was much more prominent in the ASD group than in the non-ASD group [47]. Additionally, especially in the ASD group, the increase in FALFF in the cerebellum was accompanied by an increase in cerebellar-subcortical (striatal) functional connectivity (FC) and a reduction in cerebellar-cortical FC, suggesting that CBD seems to "tune" FC in a specific way depending on the brain region and the established connection between regions [48]. Another point highlighted by this study is that, in individuals with ASD, CBD altered FALFF in both the cerebellar vermis and the right fusiform gyrus, but FC was altered only in the vermis. This may be explained by more limited connections between the fusiform gyrus and other regions compared to the connections established by the cerebellar vermis [49]. For example, post-mortem studies have observed reduced integrity of the gray-white matter boundary in the fusiform gyrus of individuals with ASD [50].

The neurobiological basis of CBD's effects on FALFF and FC may be supported by the fact that CBD influences glutamatergic and GABAergic pathways, which regulate FALFF and FC [51]. It was observed that CBD's action on specific receptors can increase and reduce excitatory and inhibitory transmissions in ASD. For example, CBD's activation of the TRPV1 receptor increases glutamatergic excitation, while CBD's antagonism of the GPR55 receptor increases the firing of GABAergic interneurons [51]. Regarding the 5HT1A and 5HT2A receptors, found in both excitatory and inhibitory neurons, CBD acts as an agonist [52]. However, it was found

that these receptors are altered in individuals with ASD, with the SERT Ala56 coding variant leading to hyperserotonemia, serotonin receptor hypersensitivity, social impairment, and repetitive behavior [53]. This may partially explain differential findings in CBD response between ASD patients and neurotypicals [54]. Other explanations for these differential findings may include reduced expression of GABAergic receptors in the fusiform gyrus of ASD patients [55], as well as reduced levels of glutamic acid decarboxylase (an enzyme that converts glutamate to GABA) and Purkinje cell inhibitory cells in the cerebellar vermis of ASD patients [56].

Finally, another review included in this work [57], based on studies selected by its authors, concluded that CBD, through the inhibition of fatty acid amide hydrolase (FAAH), an enzyme that catalyzes the hydrolysis of AEA into arachidonic acid and ethanolamine [58], increases levels of the endocannabinoid AEA, which is reduced in ASD, and decreases CB2R expression. This underscores its importance in reducing some ASD symptoms. Additionally, CBD exhibits anti-inflammatory properties, reducing levels of pro-inflammatory cytokines, and contributes to a neuroprotective microglial phenotype [59].

CONCLUSION:

In Autism Spectrum Disorder (TEA), cannabinoid derivatives have been demonstrating effectiveness in controlling behavior and irritability. However, as of now, there is no FDA-approved product for regular use. Despite the relevance of the topic, studies addressing this theme are still scarce, and more scientific evidence is needed. It can be asserted that the use of cannabinoids for TEA, overall, has shown to be safe and effective, serving as an alternative option for patients with a low response to traditional treatment modalities.

Future clinical studies should examine the efficacy of different CBD dosage ranges in a larger number of patients and in both sexes, establishing target plasma levels for CBD across various indications.

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