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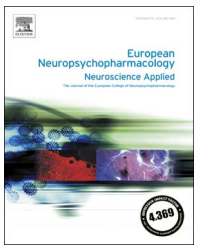

# Cannabinoids in attention-deficit/hyperactivity disorder: A randomised-controlled trial

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**Abstract**
Adults with ADHD describe self-medicating with cannabis, with some reporting a preference for cannabis over ADHD medications. A small number of psychiatrists in the US prescribe cannabis medication for ADHD, despite there being no evidence from randomised controlled studies. The EMA-C trial (Experimental Medicine in ADHD-Cannabinoids) was a pilot randomised placebo-controlled experimental study of a cannabinoid medication, Sativex Oromucosal Spray, in 30 adults with ADHD. The primary outcome was cognitive performance and activity level using the QbTest. Secondary outcomes included ADHD and emotional lability (EL) symptoms. From 17.07.14 to 18.06.15, 30 participants were randomly assigned to the active ($n$=15) or placebo ($n$=15) group. For the primary outcome, no significant difference was found in the ITT analysis although the overall pattern of scores was such that the active group usually had scores that were better than the placebo group (Est=−0.17, 95%CI-0.40 to 0.07, $p$=0.16, $n$=15/11 active/placebo). For secondary outcomes Sativex was associated with a nominally significant improvement in hyperactivity/impulsivity ($p$=0.03) and a cognitive measure of inhibition ($p$=0.05), and a trend towards improvement for inattention ($p$=0.10) and EL ($p$=0.11). Per-protocol effects were higher. Results did not meet significance following adjustment for multiple testing. One serious (muscular seizures/spasms) and three mild adverse events occurred in the active group and one serious (cardiovascular problems) adverse event in the placebo group. Adults with ADHD may represent a subgroup of individuals who experience a reduction of symptoms and no cognitive impairments following cannabinoid use. While not definitive, this study

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provides preliminary evidence supporting the self-medication theory of cannabis use in ADHD and the need for further studies of the endocannabinoid system in ADHD.


## 1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) affects around 5% of children and 3% of adults (Polanczyk et al., 2007; Simon et al., 2009). The disorder is characterised by developmentally inappropriate and impairing levels of inattention, hyperactivity and impulsivity, commonly accompanied by emotional dysregulation, cognitive impairments and psychiatric comorbidities (Asherson et al., 2016).

One of the most common problems associated with ADHD is co-occurring substance abuse (Gudjonsson et al., 2012; Lee et al., 2011; Young and Thome, 2011). One theory posited to explain the increased risk of substance use in ADHD is that of self-medication (Bolea-Alamañac et al., 2014; Loflin et al., 2014). There are several potential points that underpin the self-medication hypothesis for substance abuse in ADHD. First, different motivations behind drug use have been reported. ADHD cases were more likely to use drugs to improve their mood and sleep, whereas those without ADHD for 'getting high' (Horner and Scheibe, 1997; Wilens, 2004), suggesting that drug use in ADHD could help to improve symptoms. Secondly, stimulant medications are the recommended first line treatment in ADHD and, alongside cannabis, stimulants are one of the most common classes of drugs of abuse in ADHD (Biederman et al., 1995; Dennis et al., 2004; Gudjonsson et al., 2012; Huntley et al., 2012). This might indicate that individuals with ADHD are more likely to use drugs that alleviate symptoms of the disorder. Thirdly, in clinical practice, it is not uncommon for adults with ADHD to report potential benefits from the use of cannabis. Descriptions of cannabis effects by ADHD patients include feeling calmer, less restless and improved sleep, while a few report that cannabis helps them to remain focused (Asherson, personal communication; Milz and Grotenhermen, 2015). One case study of adult ADHD reported improved driving skills after smoking cannabis (Strohbeck-kuehner et al., 2008), and anecdotal accounts also abound on the internet. Analysis of online forums where ADHD and cannabis use was discussed found three-times as many comments advocating for the therapeutic (as opposed to harmful) effects of cannabis on ADHD (Mitchell et al., 2016). In the US, medical professionals advocated for cannabis as a treatment for ADHD before a congressional subcommittee on drug policy (Marijuana and Medicine, U.S. House of Representatives, 2004), and a small number of clinicians prescribe or recommend medical cannabis to treat ADHD (Marijuana and Medicine, U.S. House of Representatives, 2004).

Investigating the effects of cannabinoids in ADHD may therefore shed light on the high use of cannabis among adults with ADHD. Investigations of new pharmacological targets for ADHD are also important as these may lead to the discovery of novel mechanisms underpinning the disorder and potentially the development of new treatments. In ADHD there are already effective treatments such as stimulants and atomoxetine, however these are not always effective, partial response is common and they are not always well tolerated (Bolea-Alamañac et al., 2014; Faraone et al., 2015; Leonard et al., 2004; Sangal et al., 2006). In some cases more severe adverse effects have been reported, leading to the US Food and Drug Administration (FDA) approved treatments for ADHD to carry warnings that their use could involve risks of cardiovascular effects, growth suppression and the development of psychosis or other psychiatric conditions (FDA, 2006).

Previous studies report that impairments in cognitive measures of cortical control and arousal (e.g. increased omission[1] and commission[2] errors and slowed reaction times during sustained attention and inhibition tasks) are related to cannabis use (McDonald et al., 2003; Ramaekers et al., 2009, 2006; Umut et al., 2016). However, this may not be consistent with the subjective accounts of patients with ADHD, who could represent a subgroup that responds more positively to cannabinoids. For example, one study found that cognitive impairment in adulthood was associated with a childhood diagnosis of ADHD, but not cannabis use in adulthood (Tamm et al., 2014).

The mechanism for any potential therapeutic effects of cannabinoids in ADHD is unknown. One possibility is that cannabinoids enhance dopaminergic transmission (Bossong et al., 2015, 2009; Voruganti et al., 2001), which is thought to be the main mechanism by which stimulants decrease ADHD symptoms and improve cognitive performance (Leonard et al., 2004). However, the enhancement of dopamine following cannabis use is not a consistent finding (Barkus et al., 2011; Stokes et al., 2009) and other mechanisms could be involved.

Despite interest in the effects of cannabis in ADHD and the prescription or recommendation of cannabis to treat ADHD by a small number of clinicians in the US, there has yet to be an experimental investigation of cannabinoids in ADHD. We therefore set out to conduct a pilot study of a cannabinoid medication in adults with ADHD, to provide an initial evaluation of the potential effects on cognitive impairment and behavioural symptoms.

## 2. Experimental procedures

### 2.1. Study design

The Experimental Medicine in ADHD-Cannabinoids (EMA-C) study was a single centre, 6-week, double-blind, randomised placebo-controlled experimental trial of Sativex Oromucosal Spray, a cannabinoid medication containing a 1:1 ratio of delta-9-tetrahydrocannabinol (Δ9-THC) to cannabidiol (CBD). The study was conducted at the Social Genetic and Developmental Psychiatry (SGDP) centre, Institute of Psychiatry Psychology and Neuroscience, King's College London, in conjunction with the South London and the

[1]Where a participant fails to respond where a response is required during a cognitive task.

[2]Where a participant responds when a response is not required during a cognitive task.

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