REVIEW

Cannabidiol in the management of stress and anxiety

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Stress and anxiety

According to the National Institute of Mental Health "stress is how the brain and body responds to any demand."[1] How a person experiences stress, as well as the factors that contribute to stress varies from person to person. While some people may feel overwhelmed by stress, others may be able to deal with stress more effectively and may recover more quickly from a stressful event.[1-4]

Pressure at work or other daily responsibilities i.e. urgent deadlines and unbearable workload are examples of routine stress.[1] Stress may be brought on by a sudden negative change (i.e. losing a job or a divorce). However, stress can also be triggered by positive changes, for example, getting married or moving into a new house.[1-3]

Besides external stressors, stress can also be due to feelings or thoughts that cause "unrest", for example, fear of failure, fear of flying or fear of public speaking. Examples of other internal stressors ("self-induced") include uncertainty, lack of control, e.g. waiting for medical test results.[2]

Acute stress, also referred to as the "fight-or-flight" response, is the body's immediate reaction to a perceived challenge, threat or scare.[2] When stress is encountered, the body produces stress hormones and activates the immune system.[1,3]

Mild short-lived stress may be an appropriate or even beneficial reaction, by improving performance and increasing alertness. For example, stress can motivate people when they need to take a test, undergo a job interview or give a speech to a large crowd.[1,3,4] However, traumatic stress exposure (for example witnessing or experiencing an overwhelming traumatic event), can lead to the development of mental health problems such as post-traumatic stress disorder.[2,5]

When stress becomes excessive, persists over time or when stress responses are activated repeatedly, a person may feel overwhelmed or unable to cope.[3] Long-term stress or chronic stress may contribute to serious health problems and has been associated with certain gastrointestinal diseases, high blood pressure, cardiovascular disease, as well as mental disorders such as depression or anxiety.[1,4]

Anxiety is considered a normal reaction/response to psychological stress or a threat.[3,6] A certain degree of anxiety is considered to be positive (adaptive). However, when it occurs frequently, at inappropriate times and interferes with normal activities, it could lead to anxiety-related disorders.[6] Figure 1 demonstrates how anxiety affects performance:

- Before the peak of the curve:
  - Performance efficacy increases proportionally as anxiety increases.[6]
  - Anxiety is considered adaptive; it may help prepare a person so that functioning is improved in stressful situations.[6]
- Beyond the peak of the curve:
  - Anxiety is considered maladaptive; it impairs functioning and causes distress.[6]

The role of cannabidiol (CBD) in the management of stress and anxiety

The *Cannabis* plant contains more than 80 cannabinoids. Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two most studied cannabinoids.[7] It has been shown that CBD has very different effects (generally opposite) to those of THC.[8] THC
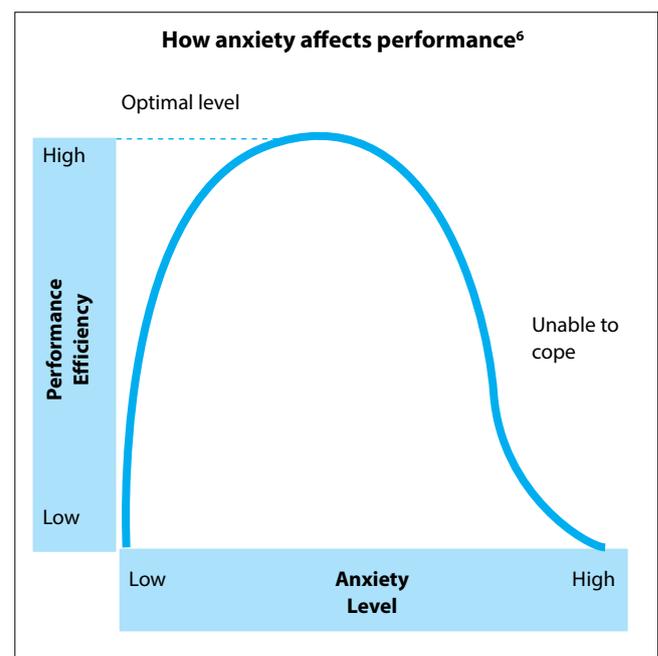

Figure 1: How anxiety affects performance. (Adapted from the MSD Manual Consumer Version [Known as the Merck Manual in the US and Canada and the MSD Manual in the rest of the world], edited by Robert Porter. c2020. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc, Kenilworth, NJ. Available from: http://www.msdmanuals.com/consumer).[6]

is the main psychoactive component in cannabis. In contrast, CBD is not psychoactive, does not appear to trigger a "high" and does not display effects suggestive of dependence or abuse potential.[8-10]

CBD has attracted considerable interest in the medical field due to its favourable safety profile and its use has been theorised for an array of medical conditions from inflammatory conditions and migraines to anxiety and depression.[5,9,11]

While CBD has no effect on heart rate or blood pressure under normal conditions, it has been shown in animal models of stress, to reduce heart rate and blood pressure.[8]

Neuroimaging studies in humans have shown that CBD has anxiolytic effects by acting on the limbic and paralimbic brain areas, "which are known to be related to anxiety."[7,12] CBD has multiple receptors and molecular targets and works via a variety of complex pharmacological mechanisms.[11-13] It has been suggested that CBD may have a role in the management of anxiety in humans owing to its activity within the endocannabinoid system.[9]

Evidence supporting the use of CBD for stress and anxiety

In a 2011 study, Bergamachi et al. compared the effects of a simulated public speaking test (SPST) on healthy control patients (number [n] = 12; without receiving any medication) and treatment-naïve patients with generalised social anxiety disorder (n = 24; who were randomly assigned to receive either a single dose of 600 milligrams [mg] CBD or placebo). The study reported that pre-treatment with a single dose of CBD, compared to placebo, significantly reduced:

- anxiety
- cognitive impairment, and
- discomfort in speech performance.[14]

The objective of a large case series by Shannon et al. was to determine whether CBD helped to improve anxiety and/or sleep. The study consisted of 72 adults seen at a psychiatric outpatient clinic over a three-month timeframe.[10] CBD dosages ranged between 25–175 mg per day (most patients used 25 mg/day). Results from the study demonstrated that:

- Anxiety scores decreased within the first month in 79,2% of patients and this decrease was sustained during the study period.[10]
- Sleep scores improved within the first month in 66,7% of patients, but fluctuated over time.[10]

Results from studies by Zuardi et al. (test of public speaking in a real situation) and Linares et al. (simulated public speaking test), suggest that CBD induces acute anxiolytic effects with an inverted U-shape dose-response curve.[7,13] According to the authors, this effect is not fully understood and it was suggested that more studies are needed to determine the optimal therapeutic dose and precise therapeutic window of CBD for each condition.[13]

Safety-related information

The World Health Organization (WHO) reports that CBD has a good safety profile and is usually well tolerated.[8] Research also suggests that CBD is not associated with abuse or dependence potential.[8] Side-effects include (but are not limited to) somnolence, sedation, fatigue, decreased appetite, anaemia, diarrhoea, pyrexia, vomiting and abnormal results on liver-function tests (transaminase elevation).[8,15,16]

According to a review by Brown et al. approximately 50% of CBD users experienced side-effects, which "displayed a general dose-response relationship".[15]

Since CBD has its own side-effect profile, there is a possibility that concomitant use with other medicines may increase the possibility of compounding side-effects. For example, drowsiness associated with CBD may be worsened if taken concomitantly with medicines with sedative properties, e.g. benzodiazepines.[15,16]

In addition, CBD has effects on a number of cytochrome P450 (CYP450) enzymes and therefore has the potential to cause drug-drug interactions through metabolic inhibition or induction.[15] Caution should be exercised with concomitant use of CBD and medication metabolised via the CYP450 superfamily, which includes warfarin, antidepressants, antipsychotics and various epilepsy drugs.[8,9,15]

Not all CBD products are equal

Persistent issues concerning product purity and lack of product regulation for safety have been listed as potential challenges surrounding the use of CBD.[9] Discrepancies have been found with respect to the labelling of CBD products. For example, some products:[9]

- Were over- or under-labelled with regards to the CBD content.
- Contain higher levels of THC than what is listed on the label.

When recommending CBD products, the healthcare professional should emphasise the importance of using the "highest-quality products."[11] It is also important to ensure that products do not only contain hemp seed oil, which does not contain any phytocannabinoids or terpenoids (hemp seed oil contains omega-6 and omega-3 essential fatty acids, γ-linolenic acid and antioxidants).[9,11]

Conclusion

Reduced anxiety has been one of CBDs "most consistently observed effects".[7] However, the sample sizes of the majority of studies relating to anxiety and anxiety-related disorders were small and more research is needed to better understand the potential use, optimal dose and safety of CBD in the management of anxiety and stress.[7,9,13]

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