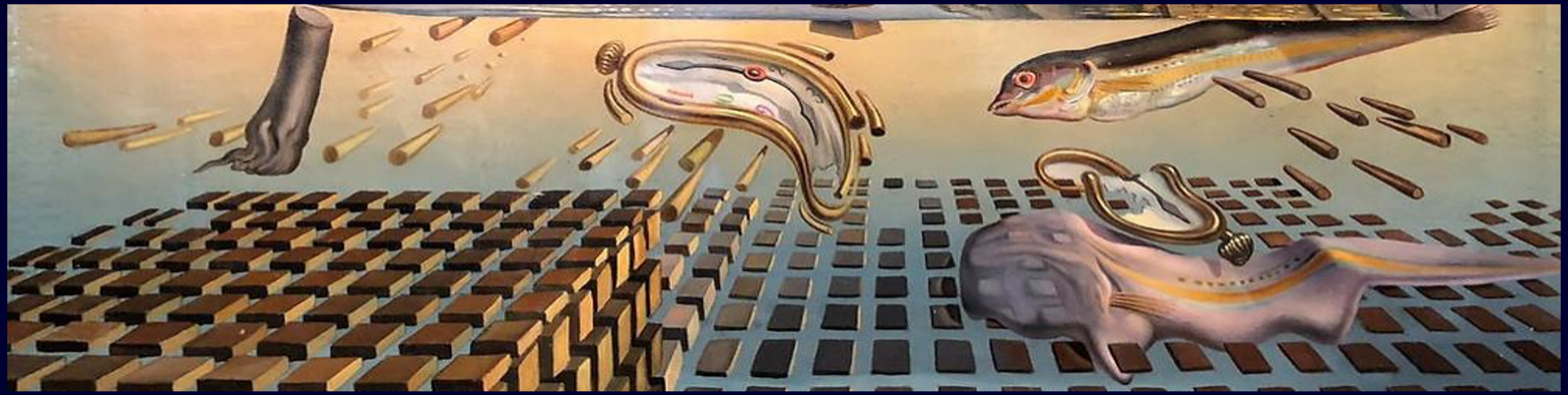
Patients Out of Time vs Patients Out of Patience



Cannabis in Mental Heath

BRYAN KRUMM, CNP

Abstract

Cannabis has been used to improve mood and emotional function for thousands of years.

Research has started to elucidate the the underlying neurobiological mechanisms by which Cannabis exerts psychotherapeutic effects. However, much remains to be learned.

Abstract

This presentation explores the known mechanisms underlying the therapeutic value of Cannabis in treating psychiatric disorders.

It also discusses historical barriers to research and makes recommendations for future areas of research needed to develop best practice standards of care.

Introduction

Treatment of psychiatric disorders is difficult and current pharmaceutical treatments for psychiatric disorders are largely ineffective (1,2)

Psychiatric disorders involve entral neurotransmitter imbalances and neuroanatomical disruptions that combine with dysregulation of immune, autonomic, endocrine, and cardiovascular function.

Introduction

Patients with psychiatric disorders are at significantly increased risk for suicide (49) and according to the Centers for Disease Control and Prevention, there were 45,979 suicides in 2020 (50).

Dysfunction of endocannabinoid signaling has been observed in the brains of suicide victims and targeting the endocannabinoid system has been proposed as a potential treatment for suicidal behavior (51).

Introduction

States that have legalized Medical use of Cannabis have seen decreasing trends in suicide rates while States without access to Medical Cannabis continue to show an upward trend. (52).

Introduction

Millions of anecdotal reports, numerous scientific reviews and dozens of clinical trials have demonstrated “conclusive evidence” that Cannabis is safe and effective for medical use.

I’ve helped to empower thousands of patients to reduce or eliminate the use of psychiatric medications

Introduction

Cannabis has been used to improve mood and emotional function for millennia.

Cannabis “jumpstarts” the endocannabinoid system and significantly reduces many of the abnormal physiological stress responses seen in psychiatric disorders (1)

To date, 47 States have approved the use of some form of Medical Cannabis.

Introduction

Due to its low toxicity, there has never been a reported case of fatal overdose with Cannabis.

Cannabis may occasionally cause dizziness, anxiety, paranoia, dry mouth, fatigue or weakness, tolerance to most adverse reactions develops rapidly.

Introduction

Cannabis is generally well tolerated and has been shown to decrease anxiety, improve sleep, stabilize and elevate mood, reduce or entirely eliminate nightmares, reduce flashbacks, reduce both positive and negative symptoms of psychosis, improve symptoms of dementia, improve concentration and treat eating disorders

Introduction

Cannabis remains in the most restrictive status of the US Controlled Substances Act

Until recently its use was restricted under International Law by the Single Convention Treaty.

Clinical research has been limited and we still have to depend mostly on anecdotal evidence, or small clinical trials (3).

Introduction

The DEA is finally complying with the 2016 settlement of a Rescheduling Petition I filed in 2009

In 2021 approved 3 new federal licenses to grow Cannabis for research purposes.

DEA has also begun to ease some of the restrictions on Medical Cannabis Research.

Role of the Endocannabioid System

The ECS is a complex system of receptors, agonists and enzymes for synthesis and degradation of endocannabinoids and which helps to maintain homeostasis of multiple biological processes (3,4,5)

It has been conserved in animal species going back a far as hydras and mollusks (6,7)

Because the endocannabinoid system regulates so many systems in the human body, it is a prime therapeutic target for many disorders (8,9)

Role of the Endocannabioid System

Dysfunctional endocannabinoid signaling is intricately involved in the neurobiological processes which underlie the symptomatology of psychiatric disorders (2,10)

An ever increasing body of both preclinical and clinical evidence supports targeting the endocannabinoid system as a treatment for anxiety, stress disorders, PTSD, depression, bipolar disorders, dementia, autism, attention deficit disorder and psychosis (11,12,13,14).

Role of the Endocannabioid System

Cannabinoids and other substances which target the ECS interact with specific brain regions, including the medial prefrontal cortex, amygdaloid complex and hippocampus.

The CB1 receptor modulates GABAergic and Glutamatergic transmission and influences the hypothalamic pituitary adrenal (HPA) axis, immune system activation, and neuroplastic mechanisms. (15)

The ECS in Depression and Anxiety

Although it has been argued that Cannabis causes depression, significant evidence suggests that depression may lead to the onset or increase in cannabis use (16).

Cannabis has been used for treatment of depression since ancient times (17).

The endocannabinoid system helps to regulate neurotransmission, neuroendocrine, and inflammatory processes involved in depression.

The ECS in Depression and Anxiety

Cannabinoid receptors help regulate several monoaminergic neurotransmitters including serotonin, which appears to be involved in the regulation of sleep, depression, anxiety, aggression, appetite, temperature, sexual behavior, and pain sensation (18).

Low levels of serotonin in the brain are associated with depression, poor memory, and cognitive impairments and targeting serotonin is the foundation of most anti-depressant treatments (19).

The ECS in Depression and Anxiety

Cannabinoids regulate 5-HT serotonergic cells by direct and indirect mechanisms which may underlie the anxiolytic and antidepressant effects induced by Cannabis.

Cannabinoid agonists and endocannabinoid enhancers increase serotonergic neuronal firing, increase serotonin release in the hippocampus and promote hippocampal neurogenesis (20).

The ECS in Depression and Anxiety

This interaction between the endocannabinoid system and 5-HT systems may underlie the anxiolytic and antidepressant effects induced by cannabis.

Cannabinoid agonists and endocannabinoid enhancers increase serotonergic neuronal firing and increase serotonin release in the hippocampus and promotes hippocampal neurogenesis (20).

The ECS in PTSD

PTSD is associated with dysfunction of the amygdala, the anterior cingulate cortex (ACC), the medial prefrontal cortex (mPFC), and the hippocampus.

Dysregulation of threat-related processing in response to trauma exposure leads to a cascade of neural changes, causing a state of amygdala hyperresponsivity, which triggers hyperarousal and vigilance.

The ECS in PTSD

Inadequate top-down control by the mPFC and ACC perpetuates the state of amygdala hyperresponsivity, increasing attention to trauma-related stimuli.

While chronic stress impairs long-term potentiation in the hippocampus, it enhances long-term potentiation in the basolateral amygdala (20).

Targeting endocannabinoid function has been shown to prevent these stress related changes.

The ECS in PTSD

The amygdala may interfere with hippocampal associative encoding via the prefrontal cortex.

CB1 receptors in the hippocampus, ventromedial prefrontal cortex and basolateral amygdala enhance extinction of aversive memories (23,24).

The ECS in PTSD

High rates of suicidal behavior have been found among patients with PTSD.

It appears that sensitization of CB1-receptor-mediated G-protein signaling in the prefrontal cortex contributes to the pathophysiology of suicide and likely contributes to suicidal behavior.

PTSD is associated with amygdala dysfunction, the anterior cingulate cortex (ACC), the medial prefrontal cortex (mPFC), and the hippocampus. Structural impairments include decreased hippocampal volume and decreased ACC volume. Dysregulation in threat-related processing in response to trauma exposure leads to a cascade of neural changes, culminating a state of amygdala hyperresponsivity, increasing attention to trauma-related stimuli. Inadequate top-down control by the mPFC and ACC perpetuates the state of amygdala hyperresponsivity, increasing attention to trauma-related stimuli.

The ECS in PTSD

Activation of CB1 receptors in the amygdala blocks reconsolidation of aversive memories and cannabinoids may help to prevent relapse after a stressful experience.

The role of the endocannabinoid system in the pathophysiology of PTSD suggests that cannabinoids may be an effective modality to treat both PTSD and suicidal behavior in patients with PTSD.

The ECS in Schizophrenia

People with schizophrenia are more likely to use cannabis than the general population and studies have proven that these patients have dysfunctions of the endocannabinoid system (25)

Subjects at high risk for psychosis with low cerebrospinal levels of anandamide are at a higher risk for transitioning to frank psychosis, and antipsychotic-naive schizophrenic patients with low cerebrospinal levels of anandamide experience more intense symptoms.

The ECS in Schizophrenia

CBD has potent antipsychotic effects and has been shown to improve both cognition and psychotic symptoms in patients with schizophrenia (27).

CBD does not activate the CB1 receptor directly, it inhibits the degradation of the endocannabinoid anandamide. Anandamide, like THC, is a partial agonist at the CB1 receptor.

In a double-blind, randomized clinical trial of cannabidiol vs amisulpride, a potent antipsychotic, both led to significant clinical improvement.

The ECS in Schizophrenia

Cannabidiol treatment is accompanied by increased serum anandamide levels which is significantly associated with clinical improvement.

Cannabidiol has a superior side-effect profile compared with amisulpride, with significantly fewer extrapyramidal symptoms, less weight gain, and lower prolactin increase.

Cannabidiol was well-tolerated and did not significantly affect hepatic or cardiac functions (28).

The ECS in Alzheimer's Disease

Endocannabinoid function modulates the primary pathological processes of Alzheimer's Disease during the silent phase of neurodegeneration: protein misfolding, neuroinflammation, excitotoxicity, mitochondrial dysfunction and oxidative stress.

Both cannabinoids and the Cannabis terpenoids limonene and alpha-pinene inhibit amyloid fibrillization in Alzheimer's (29).

THC is an acetylcholinesterase inhibitor that prevents beta amyloid peptide aggregation and also decreases agitation in dementia patients with Alzheimer's disease.

The ECS in Alzheimer's Disease

THC reduces behavioral disturbances in Alzheimers patients with improvements in nocturnal motor activity, agitation, appetite, and irritability, with no significant AEs (30).

CBD is a neuroprotective antioxidant that inhibits beta amyloid plaque formation and also prevents production of reactive oxygen species and the peroxidation of lipids.

The ECS in TBI and CTE

Acute posttraumatic glutamate release is responsible for excitotoxicity following brain injury that leads to neuronal injury, cell death and dysfunction of surviving neurons.

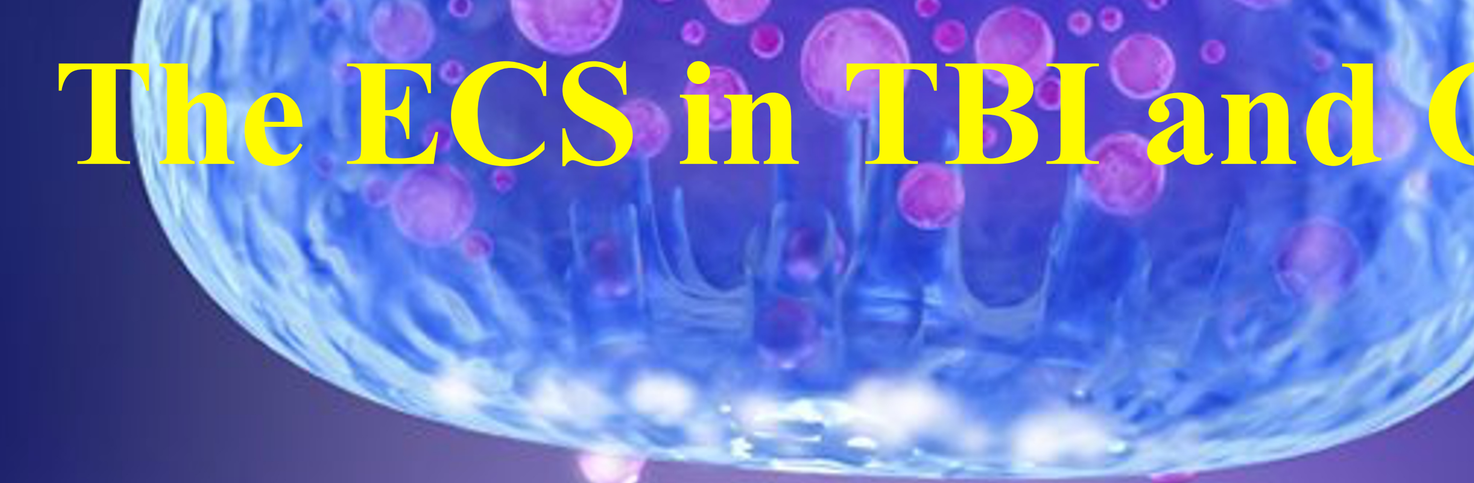
GABA modulates excitatory pathways in the brain and following injury, the loss of GABA producing cells disrupts the balance of excitation and inhibition leading to further cell injury and apoptosis.

The ECS in TBI and CTE

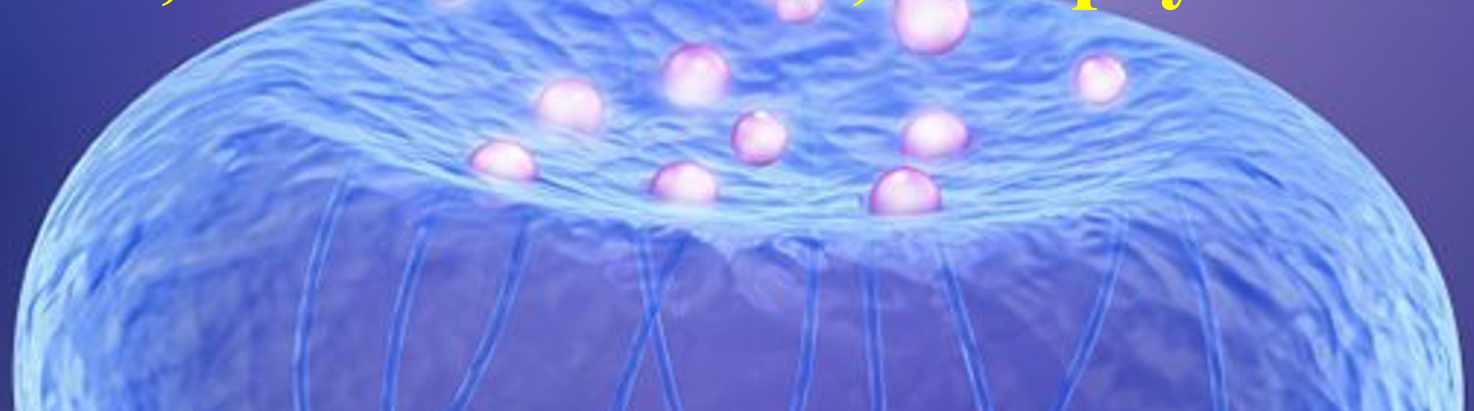
The neuroprotective antioxidant effects of cannabinoids counteract "glutamate excitoxicity," which leads to neuronal demise after traumatic brain injury (TBI).

CBD has been shown to modulate brain excitatory glutamate and inhibitory γ-aminobutyric acid (GABA) levels

The ECS in TBI and CTE



Cannabis, particularly chemovars combining THC and CBD, have been extremely helpful in treatment of chronic traumatic encephalopathy (CTE) symptoms: headache, nausea, insomnia, dizziness, agitation, substance abuse, and psychotic symptoms (29)



The ECS in Autism

Autism Spectrum Disorder is characterized by an excitation and inhibition imbalance of GABAergic and glutamatergic signaling in different brain structures.

The EC system is involved in modulating imbalanced GABAergic and glutamatergic transmission.

The ECS in Autism

Dronabinol (THC) has been shown to decrease hyperactivity, lethargy, irritability, stereotypy, inappropriate speech and treatment-resistant self-injurious behavior. (31)

The ECS in Autism

CBD enriched cannabis has been shown to significantly decrease behavioral outbreaks, improve communication decrease anxiety, reduce stress and decrease disruptive behaviors.

Supporting the Endocannabinoid System

Endocannabinoids are synthesized on demand from membrane phospholipids and depend on the levels of precursor fatty acids Omega 3 and Omega 6 which can be influenced by diet or supplementation (32).

Diet and Supplements

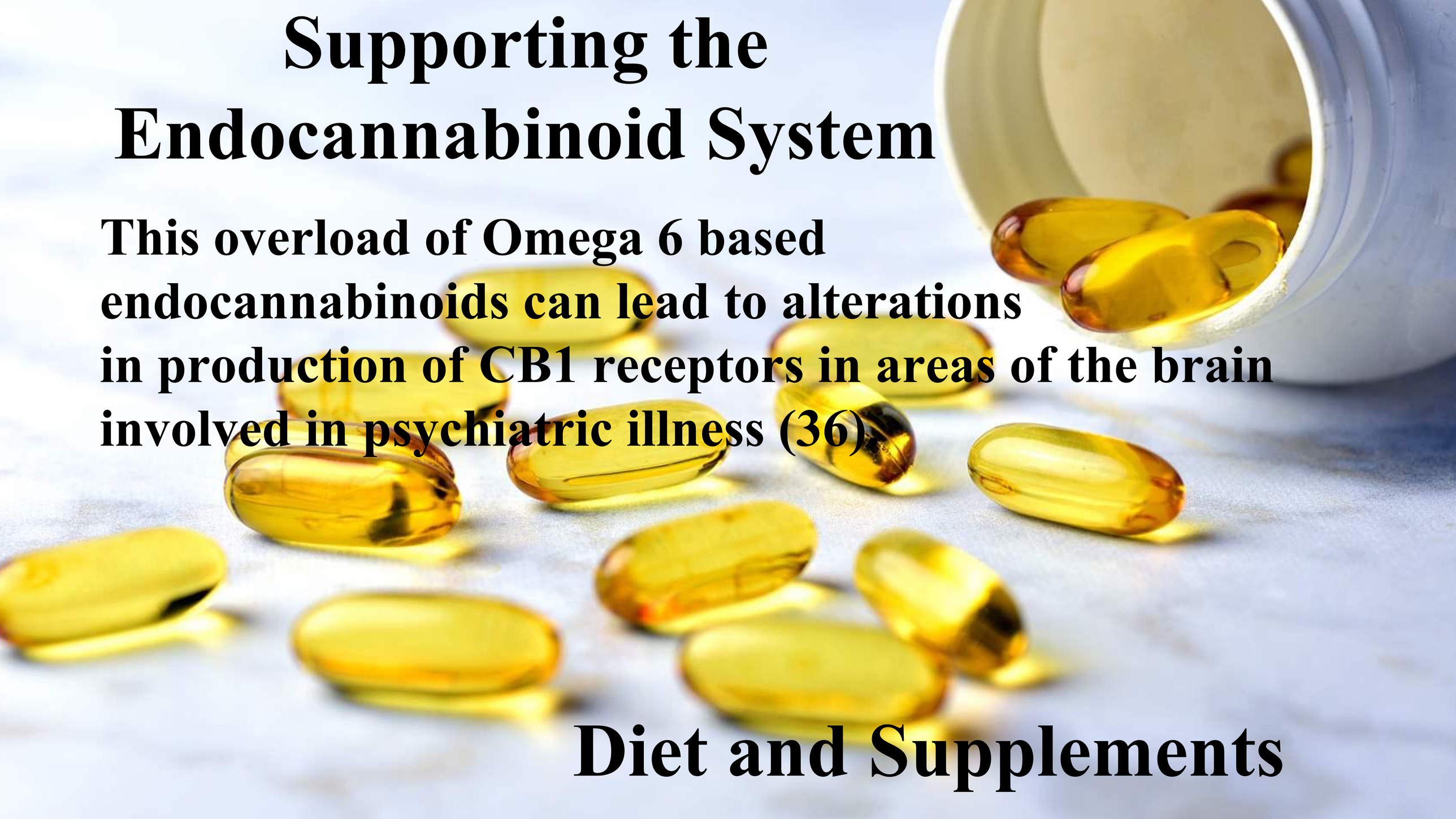
Supporting the Endocannabinoid System

Omega 3 modulates CB1 receptor gene transcription and CB1 receptor gene expression (33,34).

The typical American diet today has a 20:1 ratio of Omega 6: Omega 3, which leads to hyperactivity of the endocannabinoid system (35).

Diet and Supplements

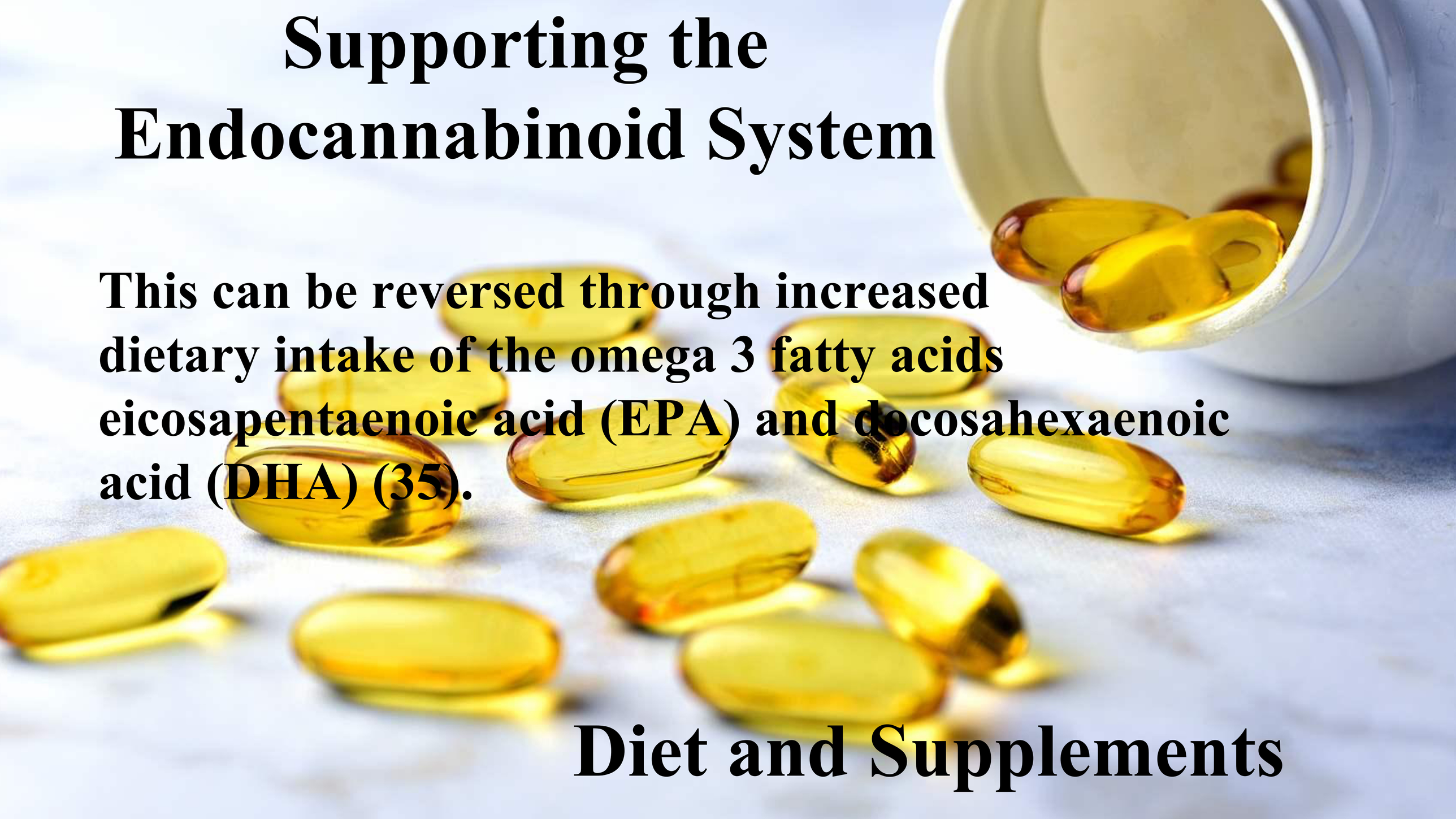
Supporting the Endocannabinoid System



This overload of Omega 6 based endocannabinoids can lead to alterations in production of CB1 receptors in areas of the brain involved in psychiatric illness (36)

Diet and Supplements

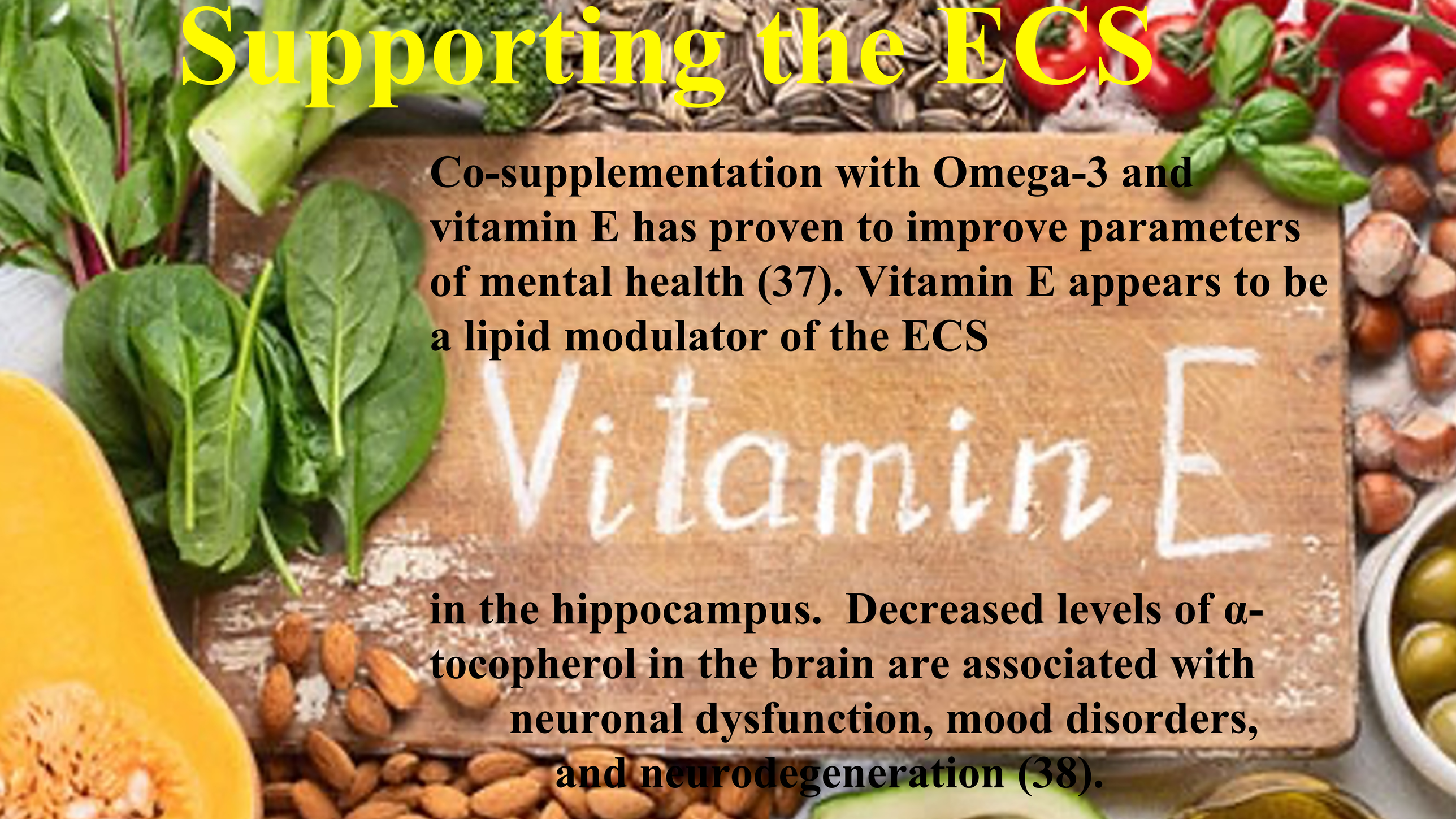
Supporting the Endocannabinoid System



This can be reversed through increased dietary intake of the omega 3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (35).

Diet and Supplements

Supporting the ECS



Co-supplementation with Omega-3 and vitamin E has proven to improve parameters of mental health (37). Vitamin E appears to be a lipid modulator of the ECS

in the hippocampus. Decreased levels of α-tocopherol in the brain are associated with neuronal dysfunction, mood disorders, and neurodegeneration (38).

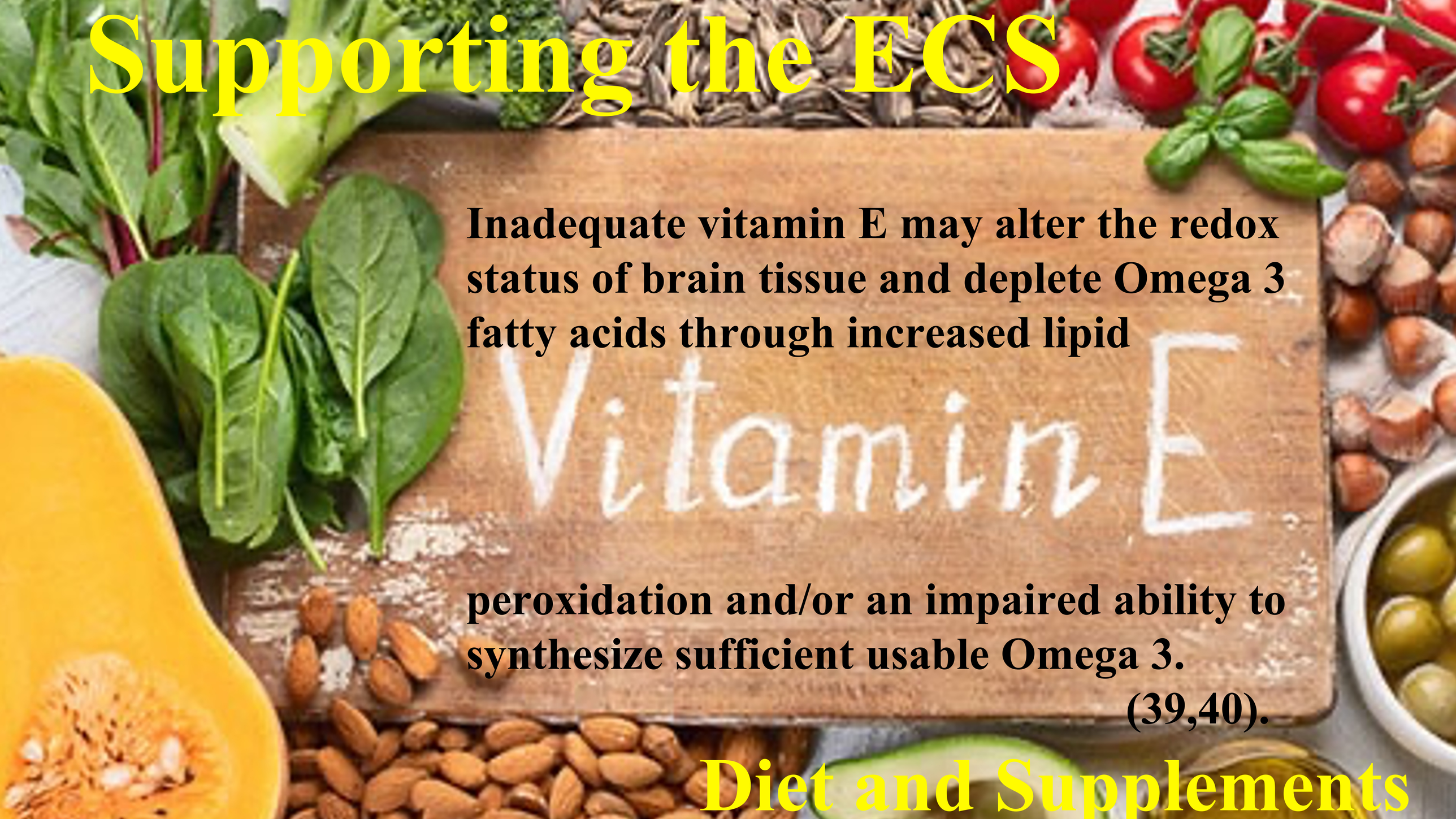
Supporting the ECS

Vitamin E helps support and modulate endocannabinoid function and works synergistically

with Omega 3 in the endocannabinoid system.

Diet and Supplements

Supporting the ECS



Inadequate vitamin E may alter the redox status of brain tissue and deplete Omega 3 fatty acids through increased lipid peroxidation and/or an impaired ability to synthesize sufficient usable Omega 3. (39,40).

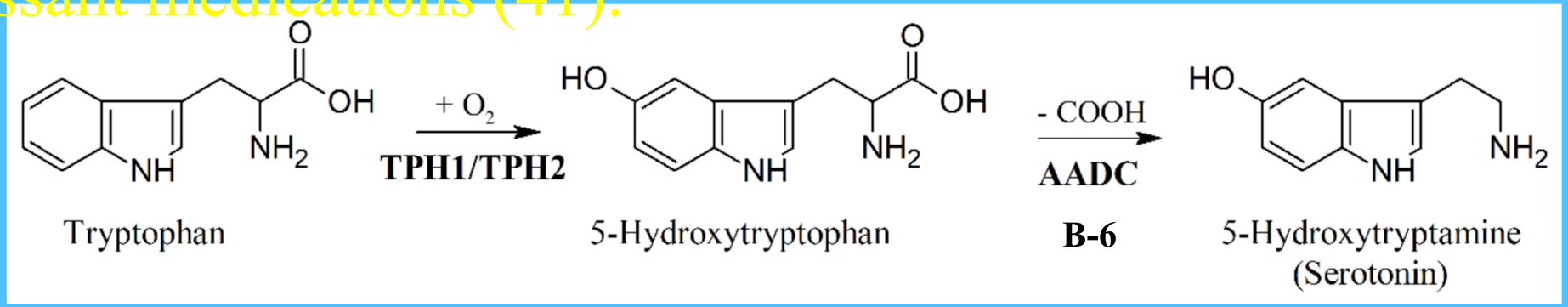
Diet and Supplements

Supporting the Endocannabinoid System

Cannabinoid receptors help regulate serotonin in the brain (18) and altered levels of serotonin in the brain are believed to underlie depressive symptoms.

Because serotonin is not able to cross the blood brain barrier, SSRIs must rely on serotonin already available in the brain to elicit a therapeutic effect which underlies the high failure rates of antidepressant medications (41).

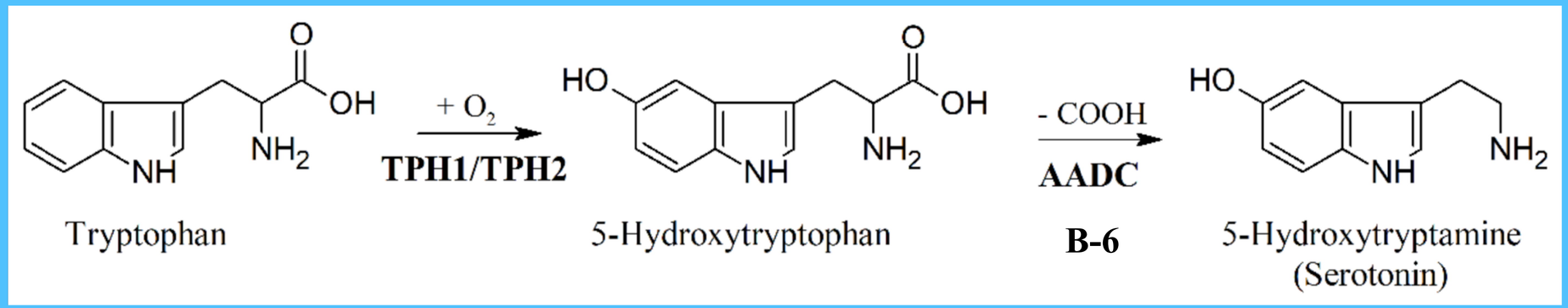
5HTP



Supporting the Endocannabinoid System

Inadequate levels of serotonin in the brain may also explain why Cannabis often fails to manage depressive symptoms. By increasing brain levels of serotonin, Cannabis may provide more effective treatment of depression.

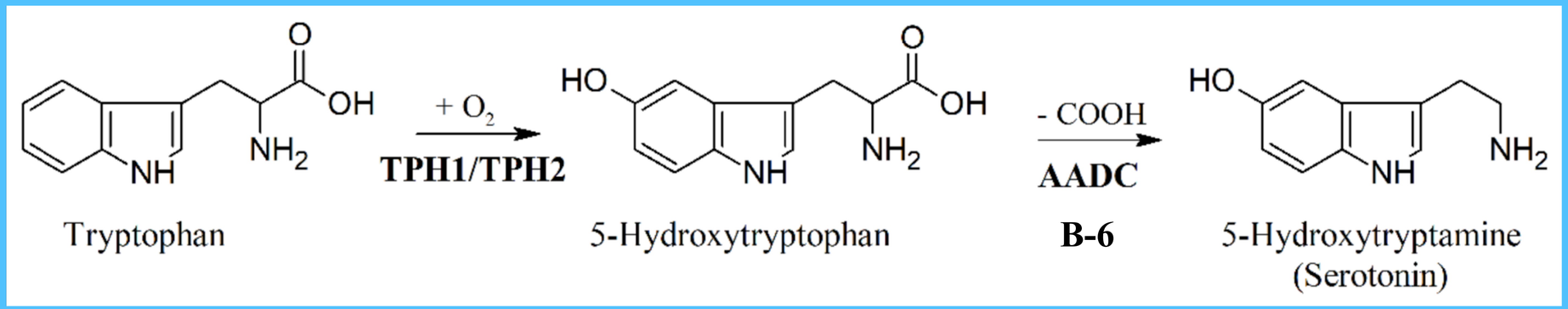
5HTP



Supporting the Endocannabinoid System

Regular exercise may help to increase production of serotonin in the brain for some individuals. 5-hydroxytryptophan (5 HTP) is an immediate precursor to serotonin which readily crosses the blood brain barrier, where it can be decarboxylated to increase levels of serotonin in the CNS (18).

5HTP

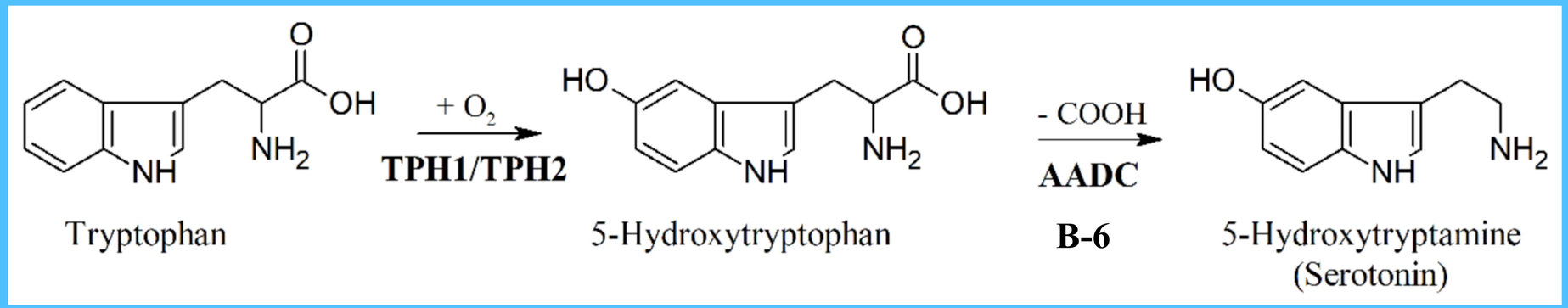


Supporting the Endocannabinoid System

5 HTP has shown promise as an antidepressant medication both by itself and as an adjunctive treatment with pharmaceutical anti-depressants (18, 41)

Combining 5- HTP with a SSRI appears quite safe in humans (41).

5HTP

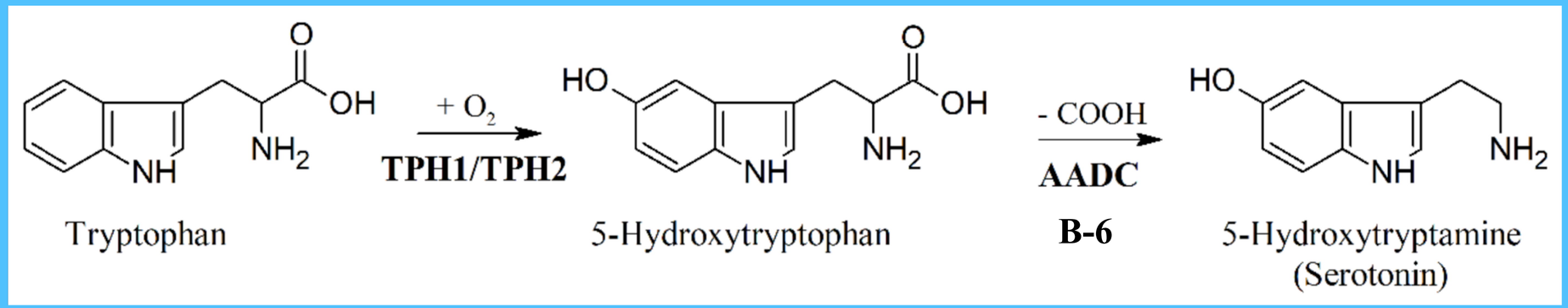


Supporting the Endocannabinoid System

In my clinical experience, 5HTP has proven to be safe and generally well tolerated in combination with Cannabis.

The combination of Cannabis and 5HTP has proven to be more effective for treating depression than either one by itself.

5HTP



Tryptophan

5-Hydroxytryptophan

5-Hydroxytryptamine
(Serotonin)

Supporting the Endocannabinoid System

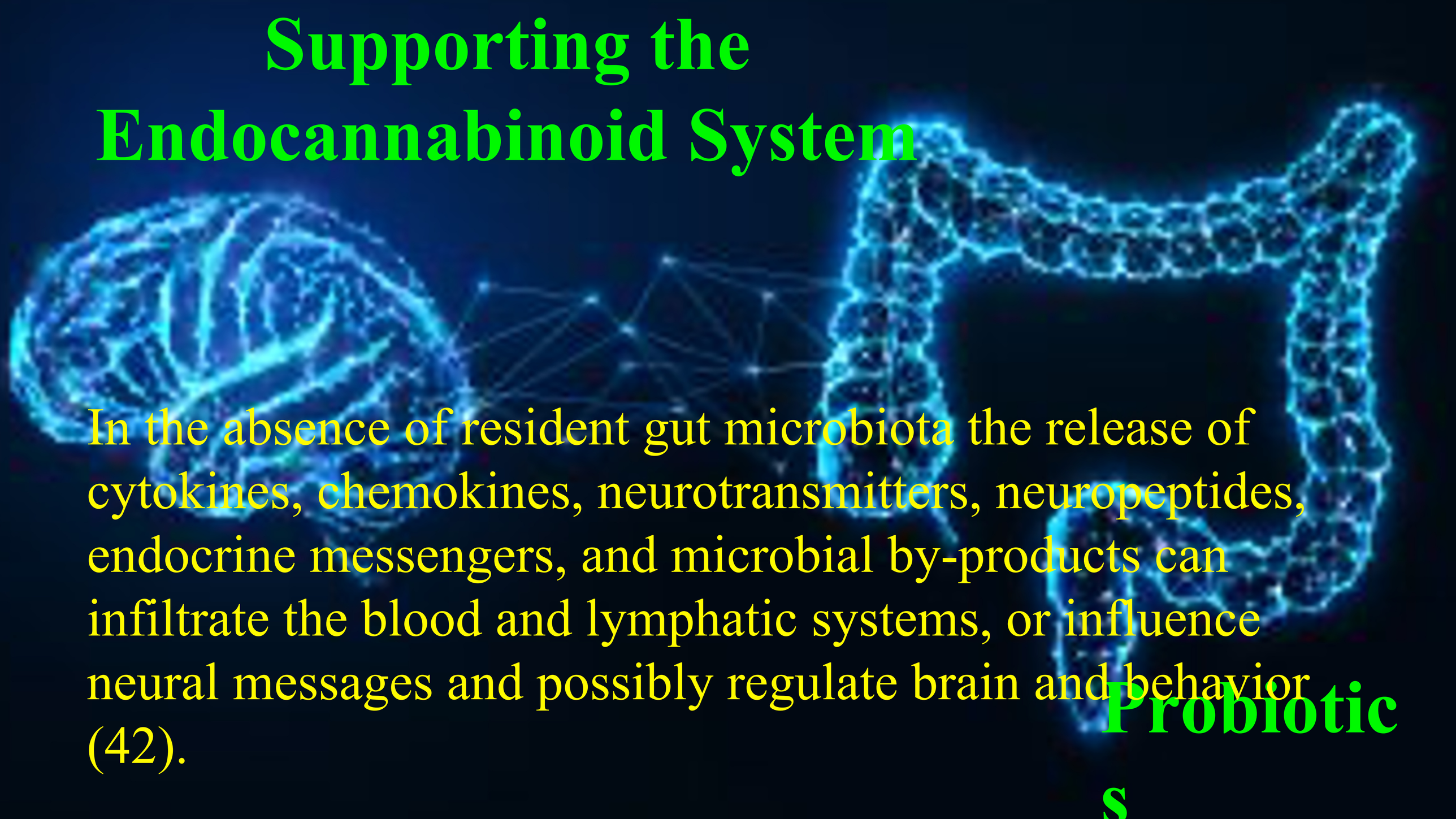
The gut microbiota has been implicated in many conditions including autism, anxiety, obesity, schizophrenia, Parkinson's disease, and Alzheimer's disease.

Activation of the mucosal immune response in the gut via exposure to bacteria and bacterial antigens induces pro-inflammatory cytokine secretion and ultimately activates the HPA axis.

Probiotic

s

Supporting the Endocannabinoid System



In the absence of resident gut microbiota the release of cytokines, chemokines, neurotransmitters, neuropeptides, endocrine messengers, and microbial by-products can infiltrate the blood and lymphatic systems, or influence neural messages and possibly regulate brain and behavior (42).

Probiotic

s

Supporting the Endocannabinoid System

Probiotics help support the gastrointestinal neuroendocrine system. Lactobacillus has been shown to increase expression of CB2 receptors which can help reduce inflammatory responses in the gut (29)

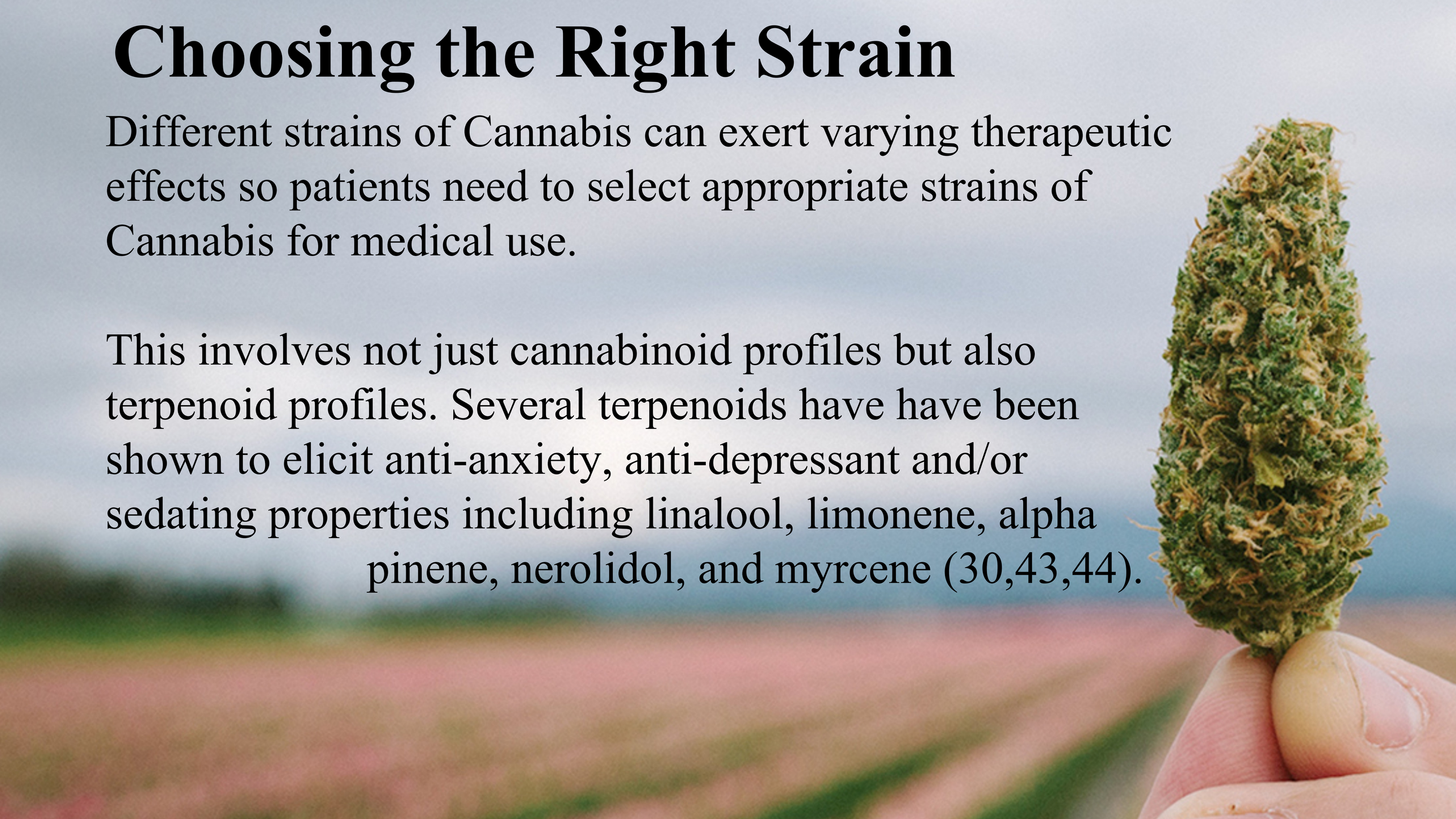
Probiotic

s

Choosing the Right Strain

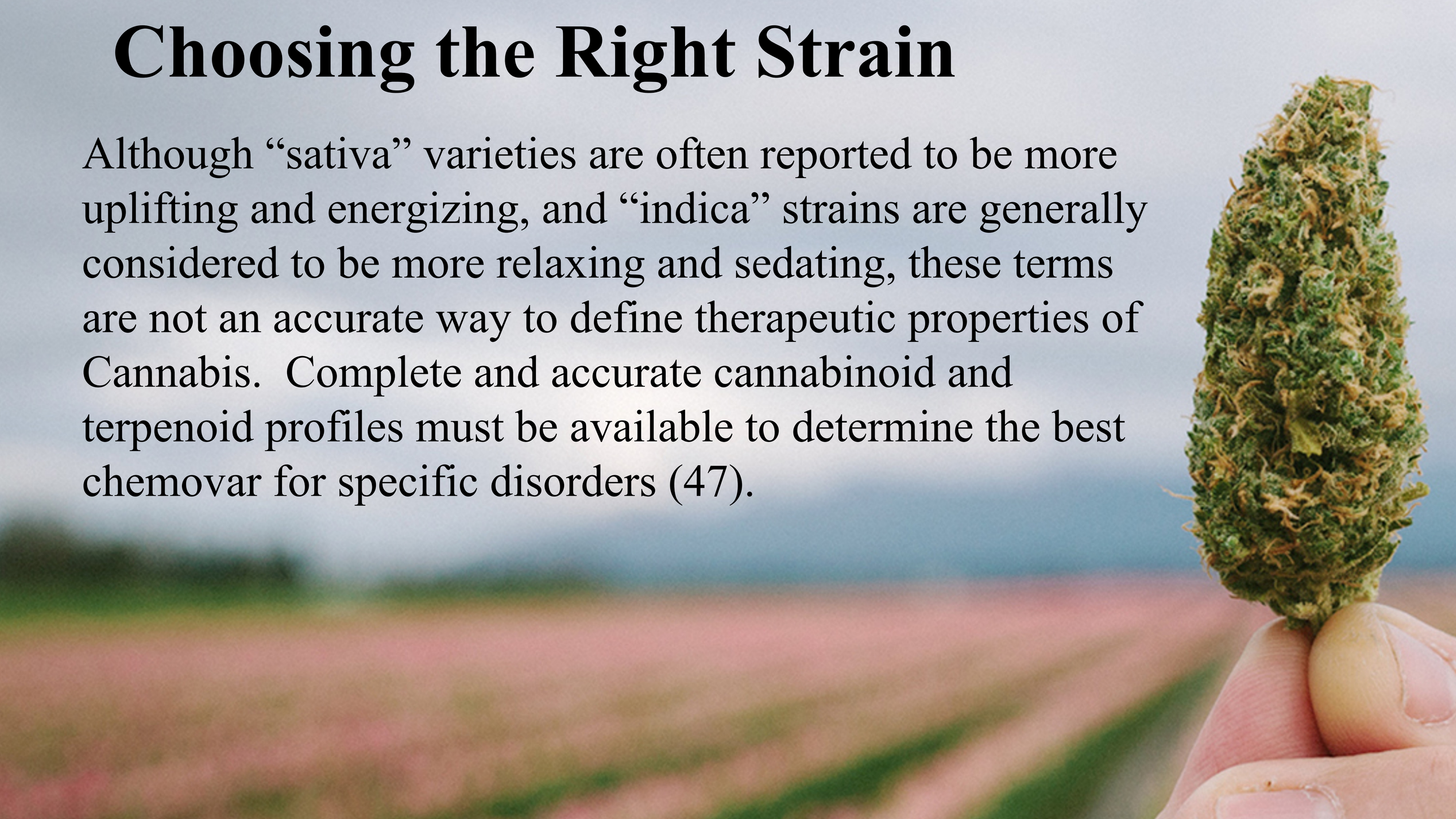
Different strains of Cannabis can exert varying therapeutic effects so patients need to select appropriate strains of Cannabis for medical use.

This involves not just cannabinoid profiles but also terpenoid profiles. Several terpenoids have have been shown to elicit anti-anxiety, anti-depressant and/or sedating properties including linalool, limonene, alpha pinene, nerolidol, and myrcene (30,43,44).



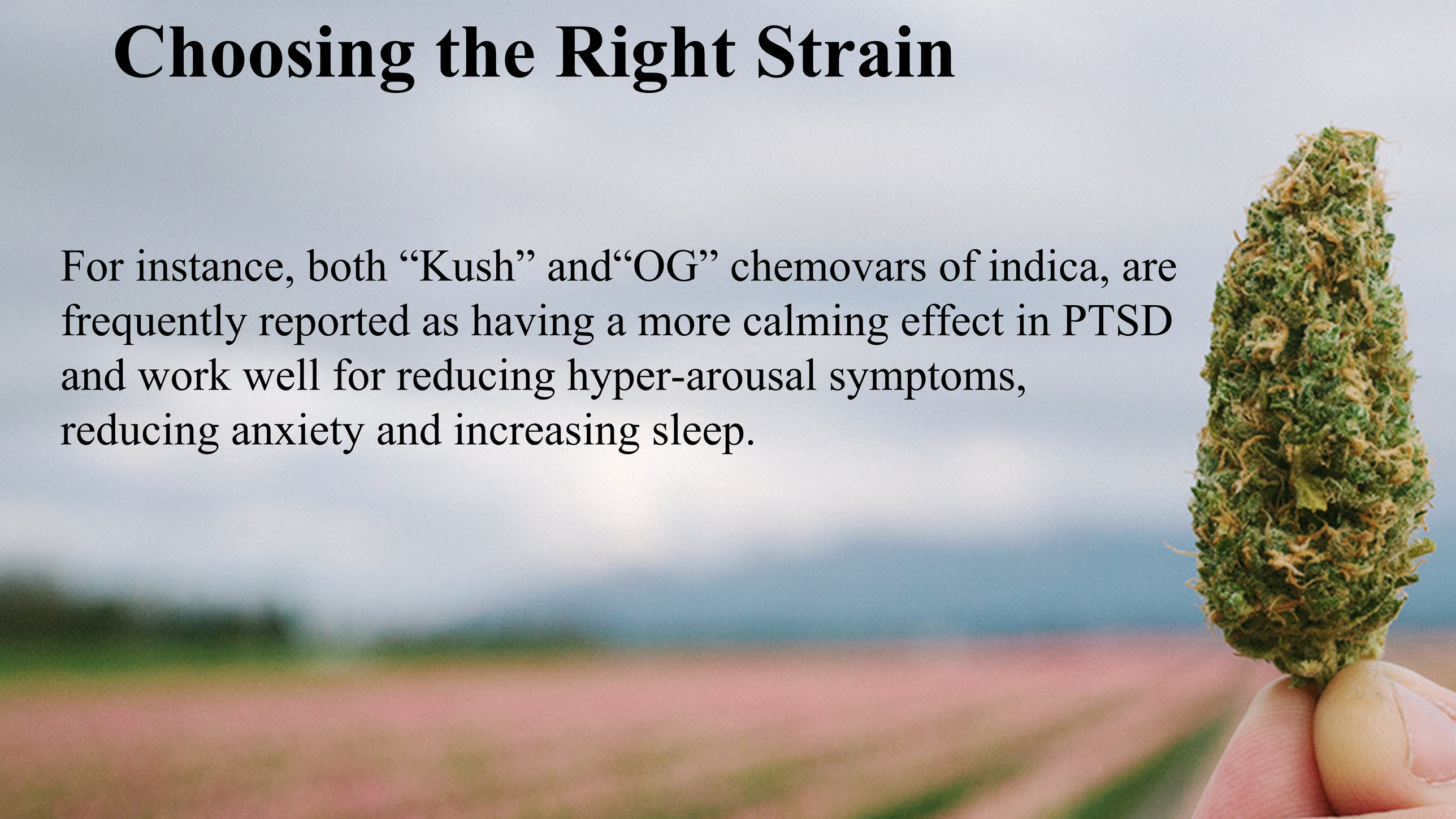
Choosing the Right Strain

Although “sativa” varieties are often reported to be more uplifting and energizing, and “indica” strains are generally considered to be more relaxing and sedating, these terms are not an accurate way to define therapeutic properties of Cannabis. Complete and accurate cannabinoid and terpenoid profiles must be available to determine the best chemovar for specific disorders (47).



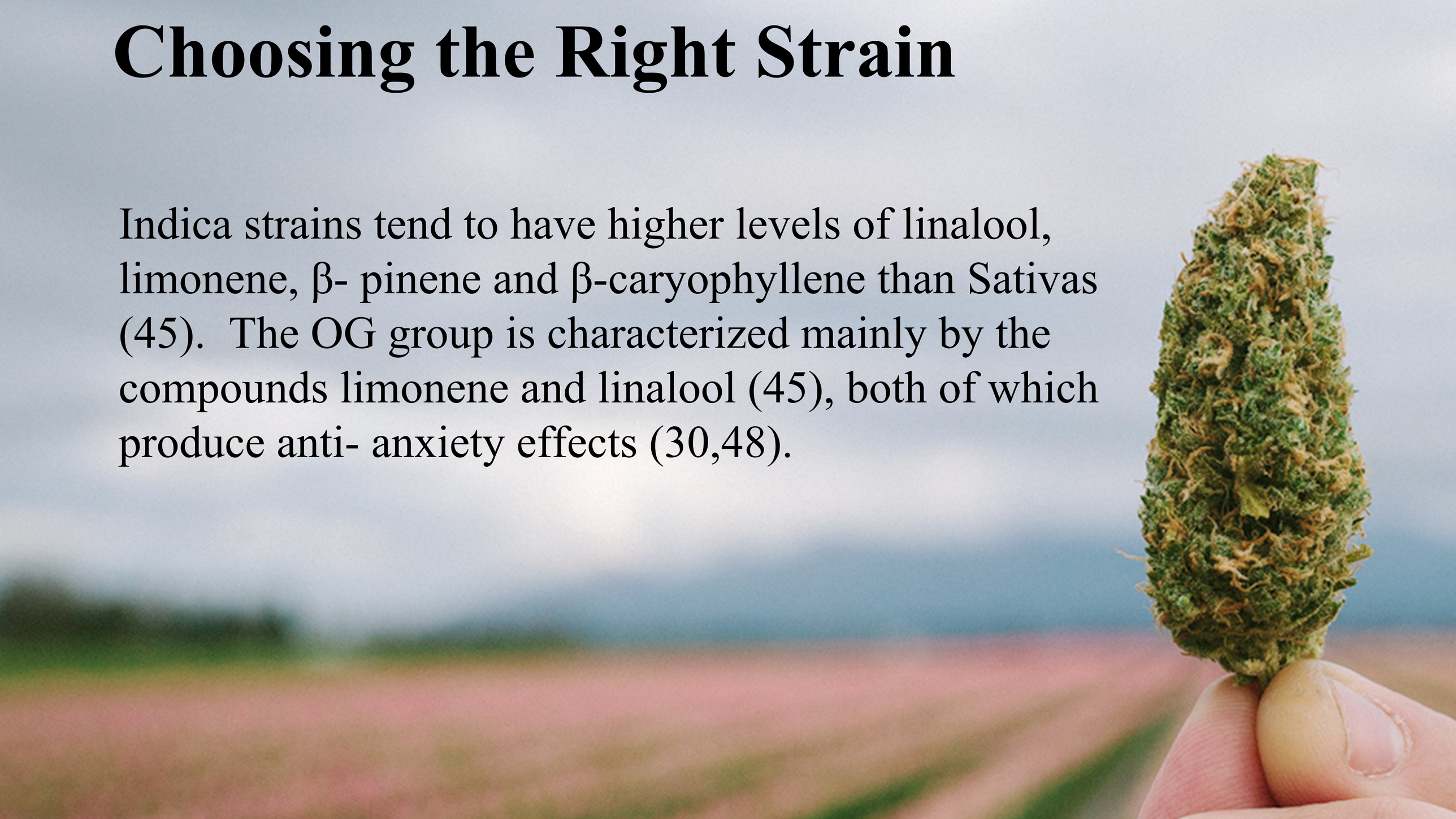
Choosing the Right Strain

For instance, both “Kush” and“OG” chemovars of indica, are frequently reported as having a more calming effect in PTSD and work well for reducing hyper-arousal symptoms, reducing anxiety and increasing sleep.



Choosing the Right Strain

Indica strains tend to have higher levels of linalool, limonene, β- pinene and β-caryophyllene than Sativas (45). The OG group is characterized mainly by the compounds limonene and linalool (45), both of which produce anti- anxiety effects (30,48).



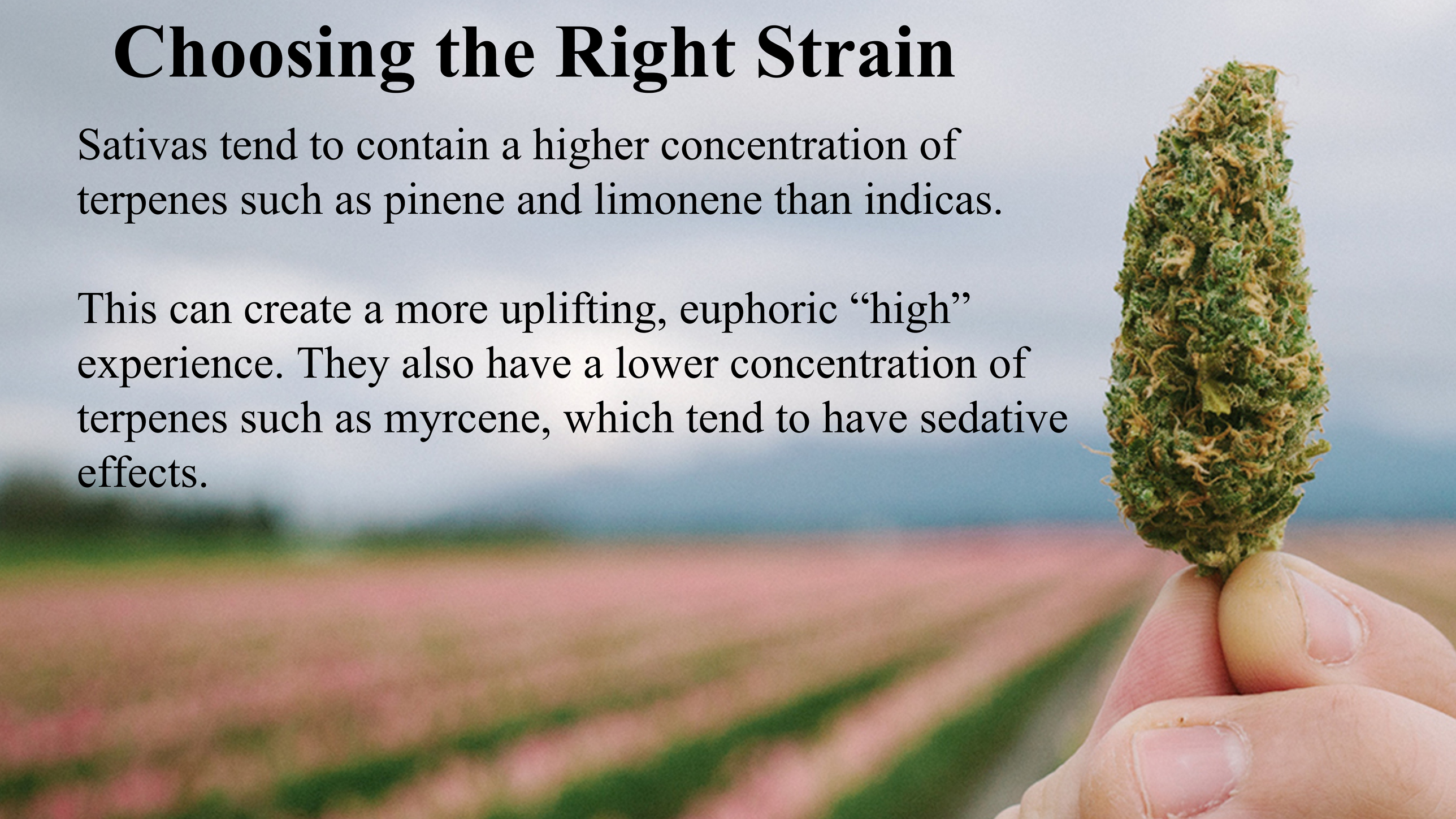
Choosing the Right Strain

The Kush group is characterized mainly by the compounds Myrcene and α-Pinene (45) which combines the sedating effects of Myrcene (30) with the anti-anxiety effects of α-Pinene (44).

Choosing the Right Strain

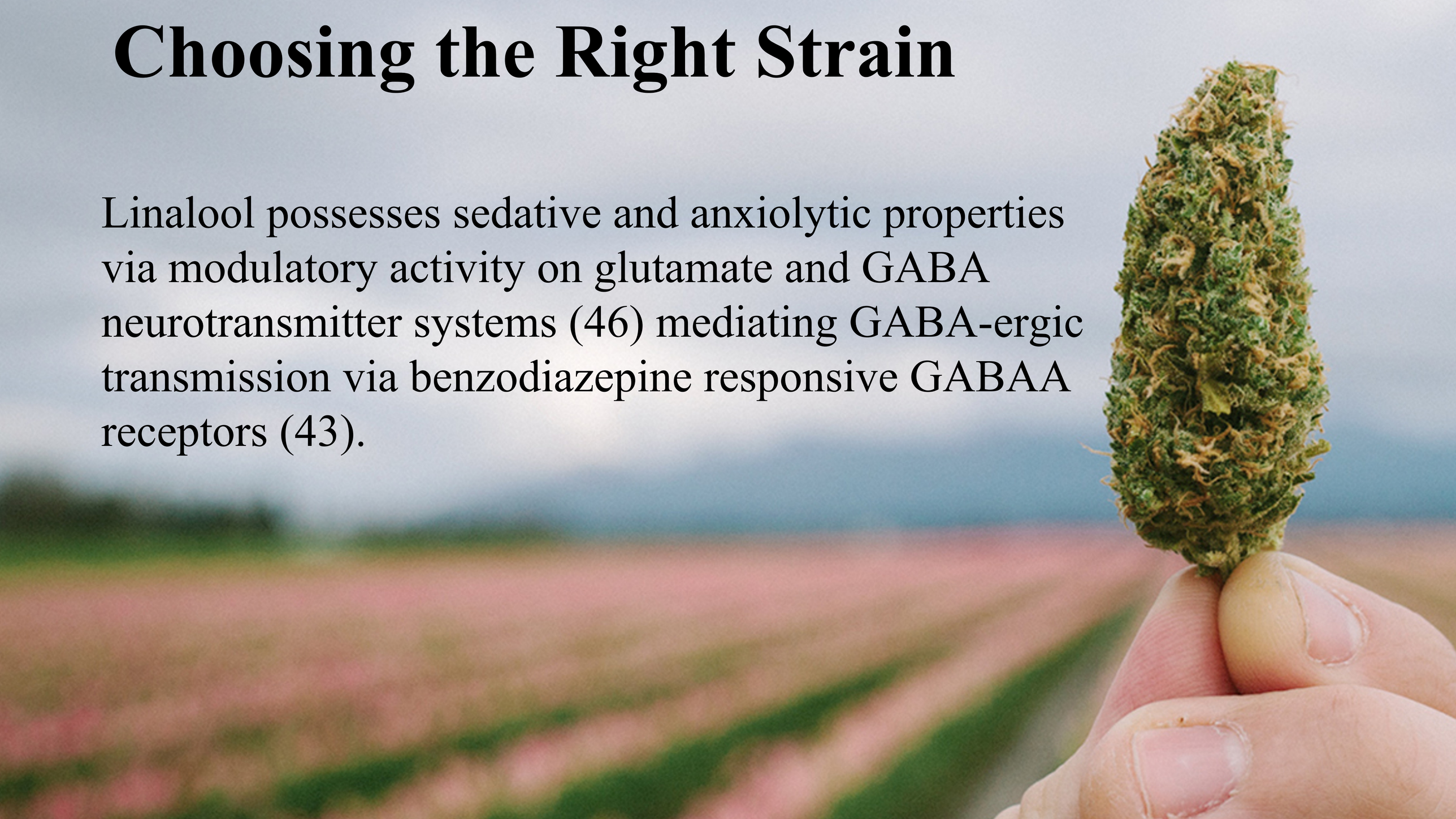
Sativas tend to contain a higher concentration of terpenes such as pinene and limonene than indicas.

This can create a more uplifting, euphoric “high” experience. They also have a lower concentration of terpenes such as myrcene, which tend to have sedative effects.



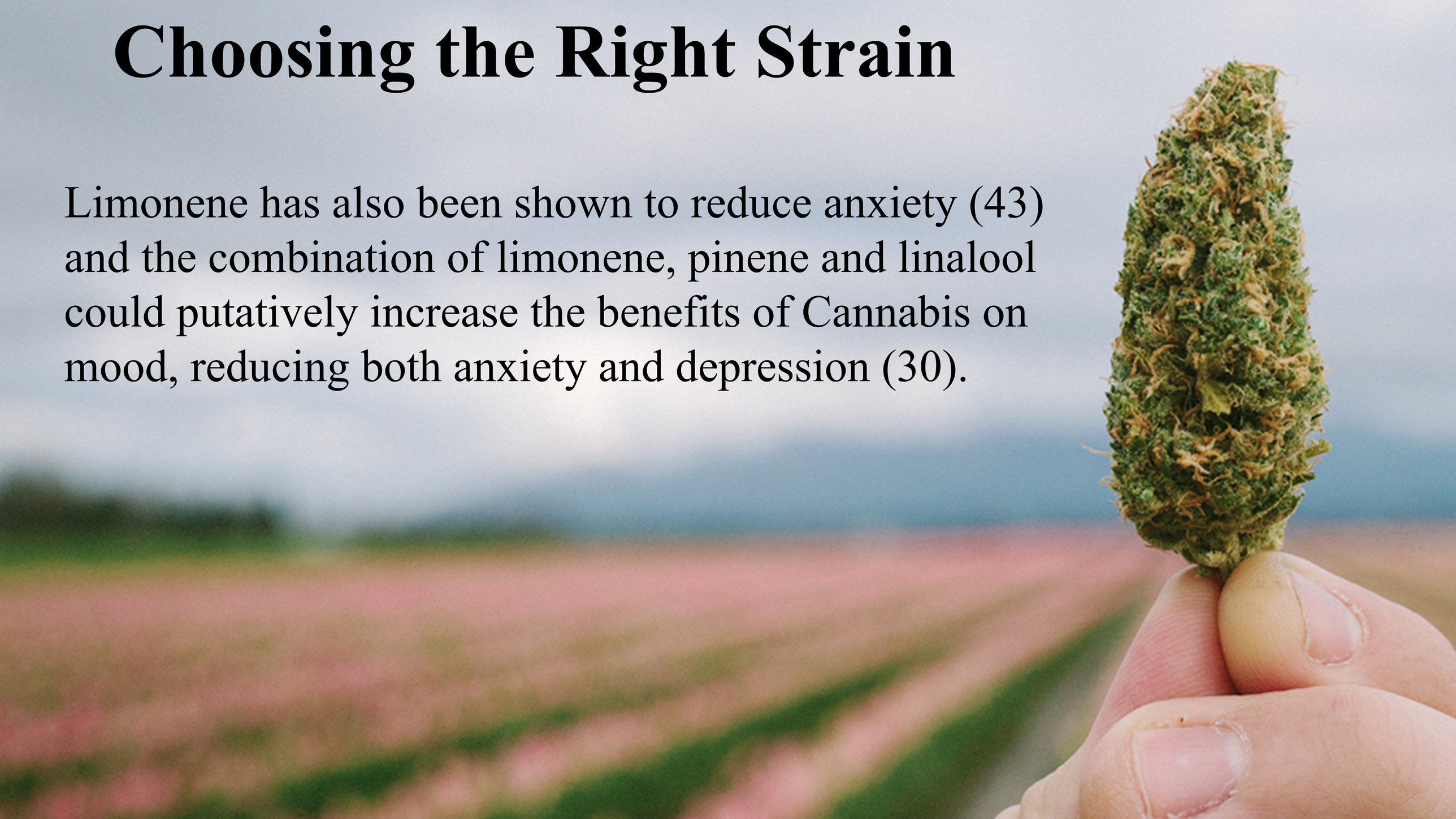
Choosing the Right Strain

Linalool possesses sedative and anxiolytic properties via modulatory activity on glutamate and GABA neurotransmitter systems (46) mediating GABA-ergic transmission via benzodiazepine responsive GABAA receptors (43).



Choosing the Right Strain

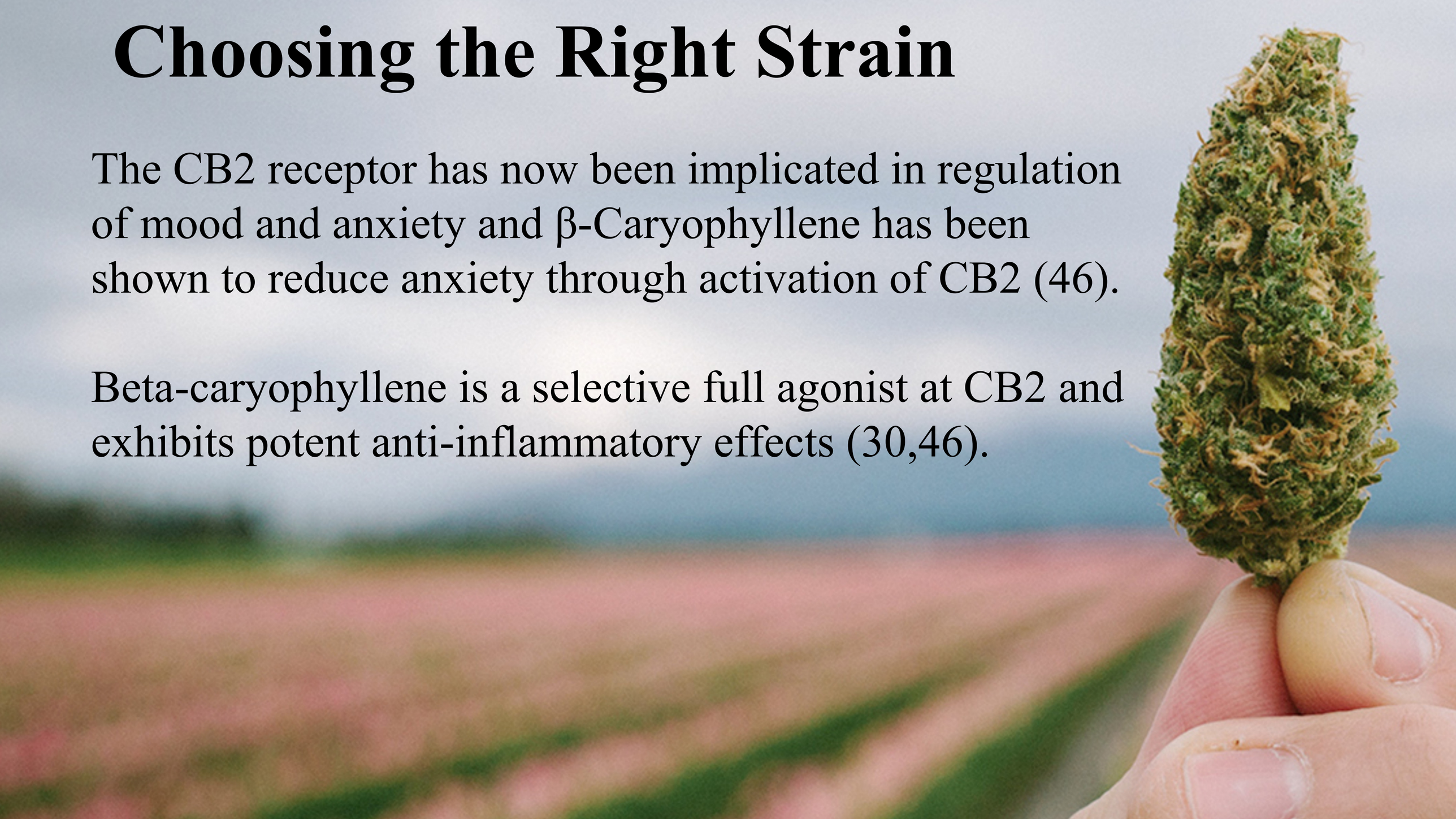
Limonene has also been shown to reduce anxiety (43) and the combination of limonene, pinene and linalool could putatively increase the benefits of Cannabis on mood, reducing both anxiety and depression (30).



Choosing the Right Strain

The CB2 receptor has now been implicated in regulation of mood and anxiety and β-Caryophyllene has been shown to reduce anxiety through activation of CB2 (46).

Beta-caryophyllene is a selective full agonist at CB2 and exhibits potent anti-inflammatory effects (30,46).

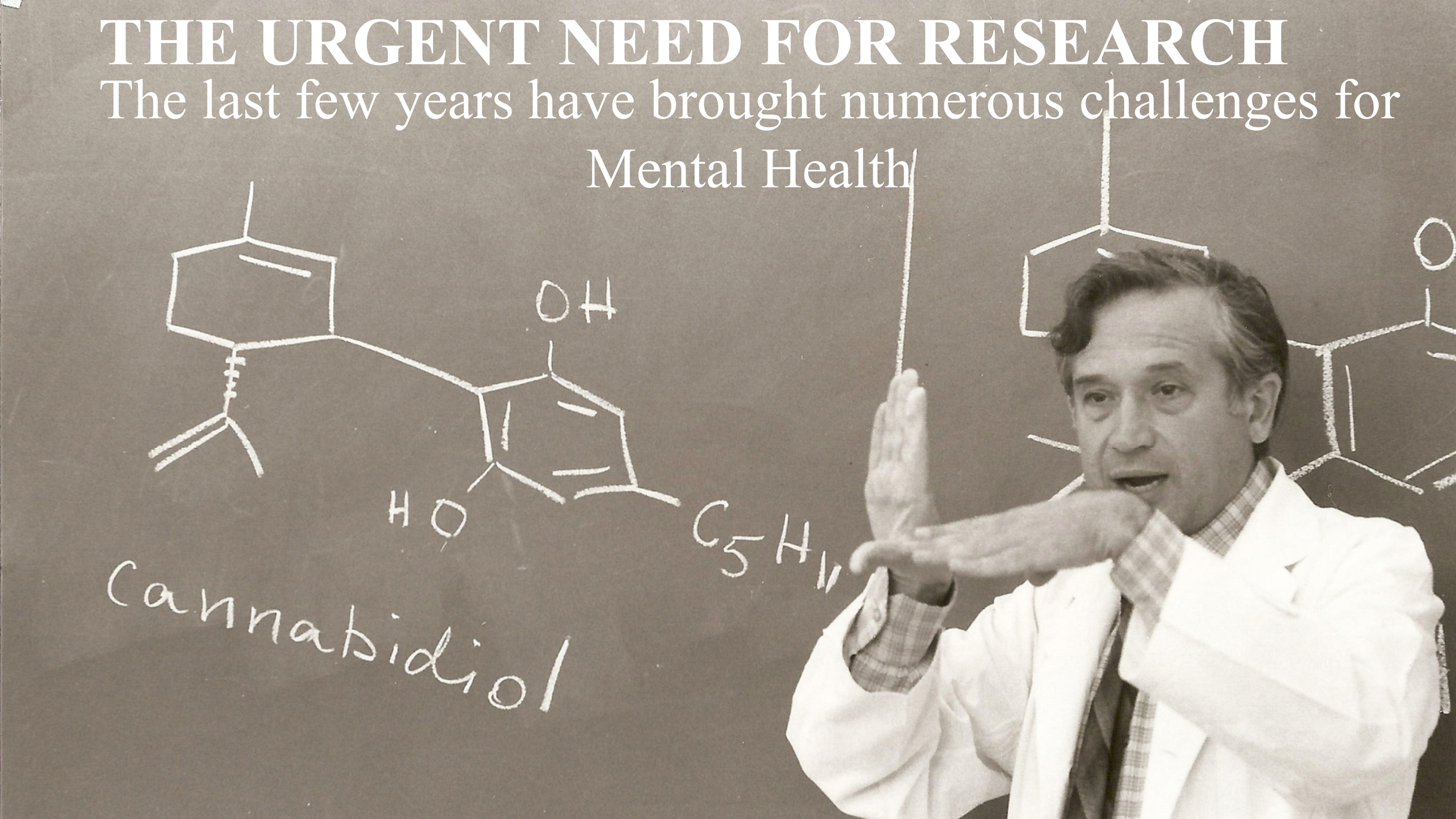


Choosing the Right Strain

β-Caryophyllene has been shown to act as a gastric cytoprotective and may contribute to both the mental clarity of pinene and the sedation of myrcene (30).

THE URGENT NEED FOR RESEARCH

The last few years have brought numerous challenges for Mental Health



THE URGENT NEED FOR RESEARCH

Covid

Deaths

Worldwide 6.3 million

US 1.01 million

THE URGENT NEED FOR RESEARCH

Climate Change

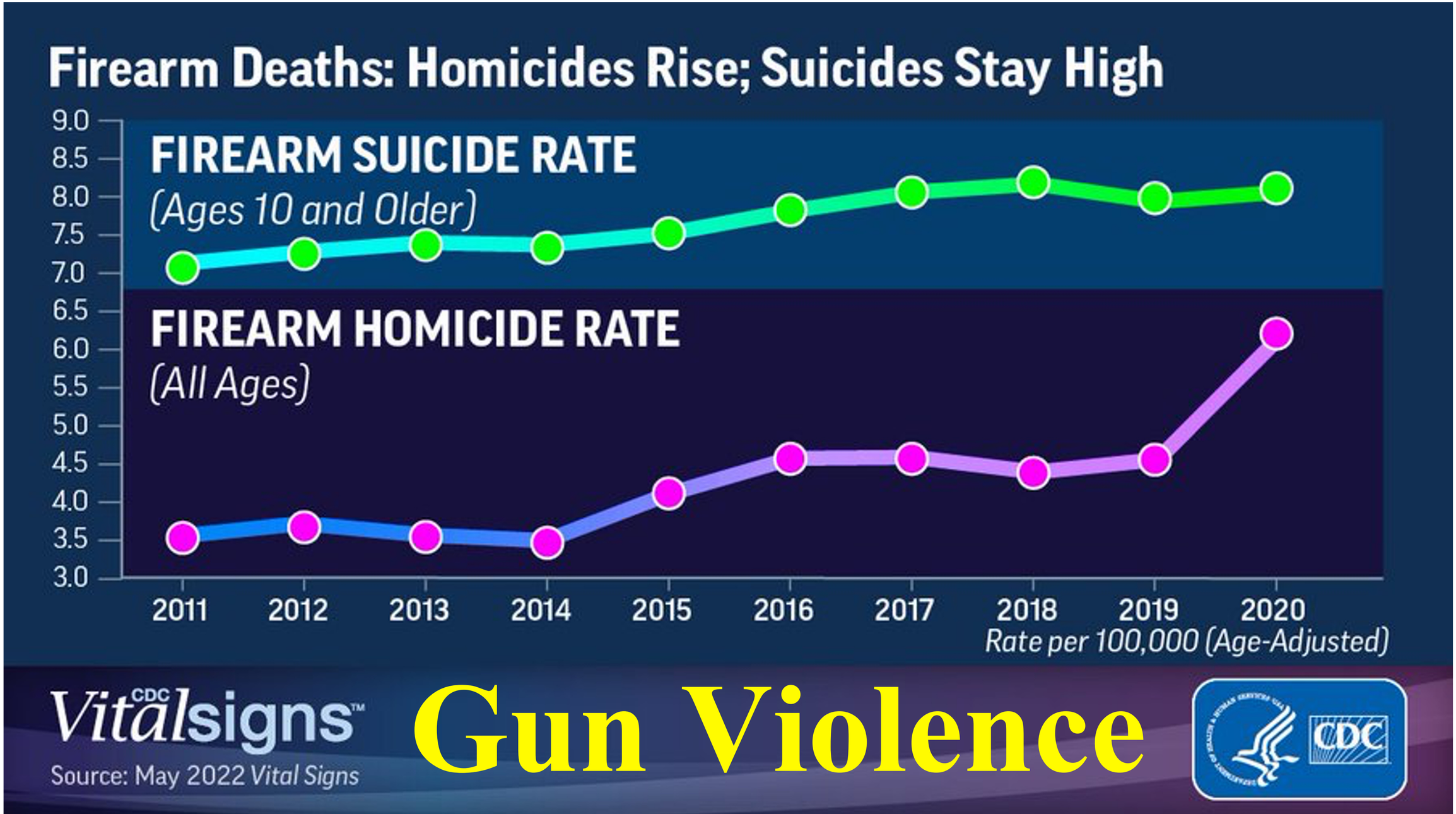
THE URGENT NEED FOR RESEARCH

Political Unrest

THE URGENT NEED FOR RESEARCH

War

THE URGENT NEED FOR RESEARCH



Future Directions

The Drug Enforcement Administration (DEA) has historically insisted that Cannabis has “no accepted medical use in the United States”, and must remain prohibited in the United States because we are a signatory to the Single Convention Treaty

Future Directions

On December 2, 2020 the United States officially recognized that Cannabis has “accepted medical use”, and joined a majority of the World in recognizing that Cannabis must be removed from the most restrictive status of the Single Convention Treaty.

Future Directions

The DEA can no longer justify Schedule 1 placement of Cannabis in the Controlled Substances Act, so we need to put pressure on the DEA, the Attornet General and our Federal Legislators to place Cannabis into an appropriate schedule.

Future Directions

Although THC (the most common phytocannabinoid in cannabis drug chemotypes) and CBD (the most common phytocannabinoid in fiber (hemp) plants are the most studied cannabinoids, many other cannabinoids have demonstrated therapeutic potential deserving of additional research.

Future Directions

CBC-has displayed antidepressant effects in rodent models.

CBG, the “mother” phytocannabinoid, has a relatively weak partial agonistic effect at CB1 but produces a greater inhibition of gamma aminobutyric acid (GABA) uptake than THC or CBD and moderates 5-HT1A suggesting antidepressant properties.

Future Directions

THCV is a propyl analogue of THC that produces weight loss, decreased body fat and decreased serum leptin concentrations.

CBN is a non-enzymatic oxidative by-product of THC, more prominent in aged cannabis samples, which produces sedation combined with THC. (30)

Future Directions

D-limonene, common to the lemon and other citrus essential oils acts as a anxiolytic agent that increases serotonin in the prefrontal cortex, and dopamine (DA) in hippocampus mediated via 5-HT1A. It appears to act synergistically with CBD.

Myrcene is a prominent sedative terpenoid in cannabis, and combined with THC, may produce the 'couch-lock' phenomenon of certain chemotypes.

- Pinene: assessed Acetylcholinesterase inhibitor, aiding memory and acting synergistically with CBD and not with THC

Future Directions

Linalool has sedating, anxiolytic and anticonvulsant properties which may be mediated through the modulation of glutamate and GABA neurotransmitter systems.

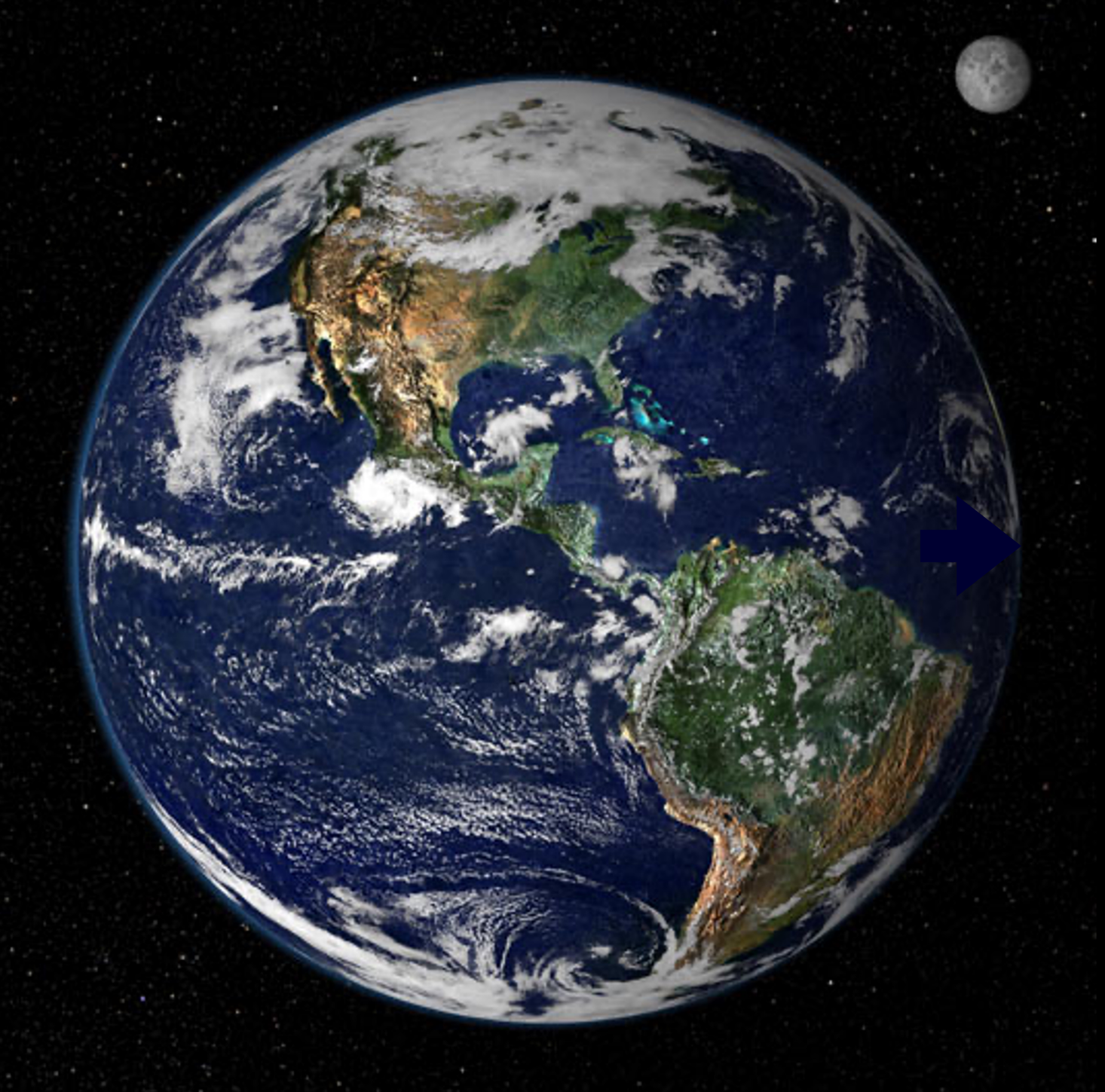
It acts synergistically with CBD and poss CBG for anxiety.

Beta Caryophyllene appears to act synergistically with CBD for addiction.

Future Directions

Nerolidol is a sesquiterpene alcohol with sedative properties.

Addition of limonene and linalool could contribute to the anxiolytic efficacy of CBD (30).



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