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THERAPEUTIC APPLICATIONS OF PSYCHEDELICS FOR ANXIETY AND DEPRESSION

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RESUM

L'ansietat i la depressió són dues malalties molt freqüents i costoses per la societat. La fisiopatologia de la depressió és una matèria molt discutida i les teories predominants són la teoria monoaminèrgica i la vulnerabilitat genètica. L'ansietat, tot i ser una malaltia amb símptomes físics, també té una fisiopatologia contestada, amb teories que inclouen neurotransmissors i hiperactivitat en certes àrees del cervell. Tot i que els fàrmacs antidepressius i ansiolítics més utilitzats siguin útils (un fet que també està contestat), tenen un inici d'acció lent, molts efectes secundaris i certes persones són resistents al tractament. Les substàncies psicodèliques són substàncies que provoquen al·lucinacions gràcies a un agonisme amb el receptor $5HT_{2A}$. Les substàncies que hem estudiat en aquesta revisió, l'ayahuasca, la psilocibina i el LSD, han fascinat a la comunitat científica i a la societat en general durant dècades i, en el cas de la psilocibina i l'ayahuasca, durant milers d'anys. Aquestes substàncies han demostrat no provocar dependència i ser generalment segures, tot i que certs efectes secundaris, molt poc comuns però greus, reclamen més estudis. En les últimes dècades s'ha començat a investigar la teràpia de l'ansietat i la depressió amb aquestes substàncies, atès que resoldrien els problemes presents amb els antidepressius actuals. A dia d'avui, l'evidència científica d'aquestes teràpies, tot i ser limitada, és molt prometedora: s'han demostrat uns efectes antidepressius i ansiolítics molt duradors després d'una sola dosi de psicodèlic. Això encoratja a realitzar més estudis clínics i potser permetre'n l'ús en certs casos especials.

ABSTRACT

Anxiety and depression are two very prevalent and costly mood disorders. The physiopathology of depression is a very discussed topic, and the predominant theories include the monoaminergic theory and genetic vulnerability. Anxiety, albeit an illness with physical symptoms, also has a contested physiopathology, the theories of which include neurotransmitters and hyperactivity in certain areas of the brain. Although antidepressant and anxiolytic medication is useful (a fact that has also been contested), it has a slow onset, many adverse effects, and some patients are resistant to treatment. Psychedelic substances are substances that create hallucinations through agonism to the $5HT_{2A}$ receptors. The substances studied in this review, ayahuasca, psilocybin and LSD, have fascinated the scientific community and society at large for the past decades, and in the case of ayahuasca and psilocybin, for millennia. It has been demonstrated that these substances do not cause dependence and are generally safe, although certain lesser common but dangerous adverse effects demand further studies. In the last few decades, studies into psychedelic treatment for anxiety and depression have sprung up, as it would solve some current antidepressant treatment problems. Nowadays, clinical evidence of these therapies, however limited, is very promising: antidepressant and anxiolytic effects were demonstrated, lasting well beyond a single psychedelic dose. This encourages further clinical studies and perhaps approval of these therapies in special cases.

INTEGRATION OF THE 3 STUDY AREAS

The main area of study is Pharmacology and Therapeutics, that includes the pharmacological characteristics of the studied substances (ayahuasca, psilocybin and LSD) and their mechanisms of action. The mechanisms of antidepressant and anxiolytic medications are included as well.

The secondary areas of study are Pharmacognosy and Phytotherapy and Physiology and Physiopathology. Regarding Pharmacognosy and Phytotherapy, the plant origins of psilocybin and ayahuasca are included, as well as their mechanisms of action. Finally, regarding Physiology and Physiopathology, the physiopathology of both depression and anxiety are encompassed.

INTRODUCTION

Depression and anxiety are very prevalent and costly disorders. It is estimated that between 1.0% to 16.9% of the world's population suffers from depression (1) and around 3.8 to 25% of all people have anxiety (2). About 50% of patients suffering from major depressive disorder receiving adequate treatment fail to respond (3), and, if patients fail to respond to two or more antidepressants, it is considered that they suffer from Treatment-Resistant Depression (4).

Even patients who respond to classic antidepressant treatment suffer from undesirable and frequent side effects, and many discontinue treatment (5). Furthermore, due to their late-onset clinical effect (6), these medications are not an ideal treatment for anxiety and depression, and alternative options are highly sought after.

Psychedelic substances have been used for millennia for religious purposes, starting at the dawn of humanity (7)**.** They are defined by their effect on the individual taking the drug, usually an altered state of consciousness characterized by distortions of perception, hallucinations, visions, dissolution of self -boundaries and "the experience of union with the world" (8).

Psychedelics have only recently re-entered pharmacological research labs worldwide, after being banned for decades, when they were thought to only be useful as psychotomimetic substances, substances that could imitate the symptoms of psychosis (9).

Even after successful studies in the fifties and sixties demonstrating that these substances could be used to treat anxiety and depression (for example, (10)), the FDA (the Food and Drug Administration) banned any pharmacological research into them in 1970 by classifying these substances as Schedule I substances, the most restrictive category of drugs (9).

This review will cover three classic serotonergic psychedelics: ayahuasca, psilocybin and LSD, and their possible therapeutic approach in the treatment of anxiety and depression.

OBJECTIVES

To present a current review of relevant theories relating to the physiopathology of anxiety and depression.

To describe the physiological and psychological actions of three classic serotonergic psychedelics (Ayahuasca, Psilocybin and LSD) and their pharmacological actions in relation to anxiety and depression.

To present a summary of the available literature on the clinical application of ayahuasca, psilocybin and LSD for the treatment of anxiety and depression.

MATERIAL AND METHODS

The following review was conducted following a bibliographic method to respond to the proposed objectives. The bibliographic sources cited include books on pharmacology and physiopathology, scientific articles, and reviews. Electronic search was carried out using the PubMed database. Initial search terms used were “LSD”, “ayahuasca”, “psilocybin”, “psychedelics” and “LSD AND depression”, “ayahuasca AND depression”, “psilocybin AND depression”, “psychedelics AND depression” as well as “LSD AND anxiety”, “ayahuasca AND anxiety”, “psilocybin AND anxiety”, “psychedelics AND anxiety”.

Regarding clinical trials involving psychedelics for the treatment of anxiety and/or depression, studies conducted before the year 2000 were excluded, and, concerning all other information sources, the most up to date sources and articles were considered.

RESULTS

I. Depression and Anxiety

A. Depression

1. An introduction into depression

Depression is a mood disorder characterized by persistent feelings of sadness and loss of interest in daily activities. Depressive disorders are classified in the *American Psychiatric Association's Diagnostic Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) into eight categories: disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (Dysthymia), premenstrual dysphoric disorder, substance or medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder (11). Even though these categories vary slightly when compared to those of *The International Classification of Diseases and Related Health Problems, 11th Edition*, (ICD11), the other gold-standard manual for the classification and diagnosis of mental disorders, the main symptoms remain the same: a "depressive mood (…) or loss of pleasure accompanied by other cognitive, behavioural, or neurovegetative symptoms that significantly affect the individual's ability to function". These symptoms include feelings of worthlessness, recurrent suicidal ideation and changes in sleep or eating patterns. It is usually diagnosed when these symptoms are present for a period of at least two weeks and can be recurrent or contained as a single episode (12).

When in a clinical trial setting, the usual way of characterising depression is with the Hamilton Rating Scale for Depression, considered the "'gold standard' for measuring depression severity" (13). It is a 17 or 21 item scale measuring factors relating to depression severity (the first 17 items) and other factors that might be tangentially related to depression but aren't directly related to its severity (14). Each item is scored from 0 to 4, and final scores range from 0-7 (normal), 8-16 (mild depression), 17-23 (moderate depression) and over 24 (severe depression) (14).

Another widely used tool to assess depression is the Beck Depression Inventory (BDI), a self-assessment tool with proven reliability and validity (15).

Mood disorders have symptom-based diagnosis, as their physiopathology is a subject of constant research. However, when a diagnosis is being considered, it is important to perform laboratory studies as other pathologies that present the same symptomatology can be diagnosed through them (16).

As we delve into the topic of psychedelic substances and their possible role in depression, it is important we first define the possible aetiology and physiopathology of depression, as we can then understand or theorise the pharmacology of psychedelics and how they could act to treat it.

2. Depression treatment: a window into the monoaminergic theory

The main theory regarding the physiopathology of depression is inferred from the pharmacology of antidepressants. This theory, commonly known as the 'Monoaminergic Theory', was originated in the nineteen-sixties by Schildkraut (17).

Commonly prescribed antidepressant act in the monoaminergic system. These antidepressants are active principles that have been shown to lower depressed symptoms. MAOIs, or Monoamine Oxidase Inhibitors, were the first of these to be approved by the regulating agencies, followed by TCAs, or Tricyclic Antidepressants. MAOIs inhibit the enzyme charged with the oxidative deamination of monoamines (MAO), a group of neurotransmitters including serotonin, dopamine, and norepinephrine.

MAO, or monoamine oxidase, is an enzyme present in most tissues whose role is to degrade both intraneuronal and intestinal amines. It exists in two different molecular forms (MAO-A, that prefers serotonin and noradrenaline, and MAO-B, which prefers phenylethylamine and dopamine). Its neuronal function is to regulate amine concentration and its intestinal function is to degrade both endogenous and exogenous amines that could be prejudicial if absorbed (17). These enzymes are located in the outer membrane of the mitochondria (18).

MAOIs, inhibiting MAO enzymes, create an accumulation of neurotransmitters in the synaptic clefts. This has long been thought to be the cause of their antidepressant effect.

TCA, or tricyclic antidepressants, act on several neurotransmitter pathways, the main one being blocking serotonin and norepinephrine uptake. This increases neurotransmitter concentration in the synaptic cleft (19).

Most of the later discovered antidepressants available to patients act in the monoamine system- SSRIs (Selective Serotonin Reuptake Inhibitors), the most commonly prescribed group of antidepressants, a group that includes sertraline and citalopram, increase serotonin availability in the synaptic cleft; SNRIs (Serotonin and Noradrenaline Uptake Inhibitors), such as venlafaxine and duloxetine, increase both serotonin and noradrenaline concentration; monoamine receptor antagonists, such as mirtazapine, block both adrenoreceptors and serotonin receptors, increasing serotonin release in the synaptic cleft (17).

The main theory derived from the effectivity of all these antidepressants was as follows: depression is brought by a deficiency in transmission within the monoamine systems, and an increased availability of monoamine neurotransmitters is the solution.

However, a few arguments contradicted this theory early on. The main ones, still in use today, are these: firstly, around a third of all depressed patients receiving antidepressant therapy are considered treatment resistant. Secondly, there is a discrepancy between fast onset neurochemical effects of antidepressants demonstrated on laboratory animals and slow onset psychological effects, as most antidepressants have a 7-21 day buffer period between starting the treatment and experiencing its psychological effects (20). From these arguments, new challenging theories emerged.

3. Genetic vulnerability and other theories

Heninger *et al*., in 1996, studied whether monoamine depletion caused depression in humans. They concluded that catecholamine depletion using alpha-methyl-para-tyrosine, a substance that blocks a norepinephrine and dopamine precursor, created no relapse to non-recovered depressed patients off medication and no depression to healthy controls. However, serotonin depletion using parachlorophenylalanine (PCPA), a serotonin synthesis inhibitor, created a relapse in depressed medicated and recovered patients off medications, but no relapse in non-recovered depressed patients off medication or healthy controls (20). They concluded that monoamines did not have a direct regulatory action on depression, but perhaps a modulatory role, since antidepressants were still efficacious (8).

Other theories include genetic vulnerability, as around 30 to 40 percent of depressions are due to genetic factors, the other 60 to 70 percent pertaining to “individual-specific environmental effects” (21). It has been theorised that there could be a specific genetic variation to the promoter region of the serotonin transporter, but genome-wide association studies have yielded no results (22). This has resulted in the idea that depression could be an amalgamation of symptoms from various identified and unidentified illnesses, and not a disorder on its own (23).

Some have also proposed that depression could be brought by a malfunction in the extrahypothalamic CRH (Corticotropin-Releasing Hormone) system, as an increase in CRH causes depression-like symptoms and CRH_1 receptor antagonists have antidepressant effects (21).

Finally, a theory stating that antidepressants work by promoting neuroplasticity has been prominent in the last few years (24), and Casarotto *et al*. found that certain antidepressants including SSRIs act by binding to the TRKB receptor (25). The tropomyosin receptor kinase B is a receptor for the the brain-derived neurotrophic factor (BDNF), a protein that promotes

neuronal plasticity. The hypothesis that antidepressants act by modulating brain plasticity would explain the slow-onset of psychological effect.

4. Do antidepressants truly work?

Parallel to these studies, others have been wondering whether antidepressants truly work. Randomized Control Trials (RCTs), the gold standard for drug trials, conclude that antidepressants are 20 to 30 percent more effectice than placebo, althought it depends on symptom severity (as symptom severity hightens, so does antidepressant efficacy) (4).

Depression diagnosis have skyrocketed in the past decades, which could be explained by a general underdiagnosis being corrected. However, antidepressant use has also increased dramatically (4).

Moreover, there are no real psychological differences between very different pharmacological antidepressant actions (4). Finally, the way we calibrate depression, the Modified Hamilton Depression Scale, for example, has questions that aren't depression-related but are, for example, sleep-related. This may be modifying scores in favor of antidepressants that create a sedative effect (4).

Another fact to be taken into account is the high relapse rate after patients stop medication treatment (4). This could be explained by the 'nocebo' effect, the opposite effect to a placebo, according to which patients would relapse because of negative expectations related to not taking their medicaction (4). Finally, there is the enormous problem of treatment-resistant depression.

Kirsch *et al*., in 2008 (26), postulated that antidepressant effect had no real difference to placebo effect in most clinical studies presented to the FDA (Food and Drug Administration). Their results have since been highly contested (27), but the review opened a window into a revision of RCTs.

On the first hand, while studying antidepressant effects of psicoactive drugs, using inert placebos is the standard. However, Penn and Tracy (4) argue that this negates the double blind intention of the clinical trial, as drug trial participants can differentiate the drug from the placebo by its side effects, thus 'unblinding' the trial. To counter this eventuality, some studies have been performed with "active placebos" that mimic antidepressant side effects (28).

Other criticisms aimed at RCTs wonder whether patients accepted into these trials represent the depressed population at large or only those with better possible outcomes (4).

After all of this, one question remains: why don't antidepressants work as well as we would like? Some studies demonstrate that socioeconomical status might be a predictor of

antidepressant treatment response (29). Indeed, Branchi *et al*. demonstrated that mice treated with antidepressants only thrived in good enviroments, and even deteriorated in negative environments (30).

All of this demonstates that further inquiries into the pharmacology of antidepressants and alternative therapies is indispensable.

B. Anxiety

1. An introduction into anxiety

According to the DSM-V, anxiety disorders include separation anxiety, specific phobia, panic disorder, generalised anxiety disorder, social anxiety disorder and agoraphobia (12). In this review, we will focus on generalised anxiety disorder.

This disorder is characterized by "excessive anxiety and worry" that does not reflect the importance of the event or subject matter the patient is worried about. They prevent the patient from functioning correctly (11).

Anxiety produced by this disorder differs from everyday anxiety by a few specific traits. Firstly, everyday worries are not so pervasive, distracting, or lasting. Secondly, everyday worries are much more manageable, and their importance correlates to how anxiety-inducing they are (11).

To be diagnosed, "apprehensive expectation" must occur in more days than not during a period of at least six months. The patient "finds it difficult to control the worry" and has at least three symptoms from a list including fatigue, muscle tension and irritability (11). These are physical symptoms, an important difference when comparing anxiety and depression, and are brought by an activation of the hypothalamic–pituitary–adrenal axis (31). These symptoms can't be explained by either medication, a medical condition, nor another mental disorder (11).

A common tool used to measure anxiety is the State-Trait Anxiety Inventory (STAI). It's a self-report instrument consisting of 40 items divided in two scales: the state anxiety scale and the trait anxiety scale. State anxiety refers to symptoms in the exact moment, how the participant feels "right now". Trait anxiety refers to ongoing anxiety symptoms, more a state of mind than a current symptom (32).

2. *Anxiety treatment*

Although not so common nowadays, the main treatment for anxiety has historically been benzodiazepines. This drug family, that includes Diazepam and Zolpidem, acts selectively on $GABA_A$ receptors by positive allosteric modulation, incrementing GABA affinity to its receptor (17). This increases GABA-activated chloride channel openings (17), rapidly improving anxiety symptoms (33). However, benzodiazepine drawbacks are also important, as they can create dependence and even death by overdose when taken with other central nervous system depressants such as alcohol (17). Because of it, and the myriad of side effects they create, benzodiazepines are mostly used as short term relief for acute anxiety and to treat insomnia (17).

Nowadays, the first-line pharmacological treatment for anxiety disorders is an antidepressant treatment that includes either SSRIs or SNRIs (33). Here, as in depression, these medications have a delayed onset of psychological effect, but their clinical benefit has been demonstrated (34). Moreover, the importance of the serotonin circuit in anxiety has been proven by administering mCPP, a serotonin receptor ($5\text{-}HT_{2C}$) agonist. When given in a clinical trial setting, mCPP inhibits serotonin release in the brain and causes anxiety and anger in patients already diagnosed with GAD (35).

3. *The physiopathology of anxiety*

Although anxiety presents physical symptoms, the underlying physiopathology is still an important and ongoing area of research, and, as with depression, a few theories have been put forth.

The first theory is based on neuroimaging. It has been reported that patients suffering from anxiety disorders suffer grey matter loss in multiple areas of the brain, a symptom associated with inferior executive functioning (36). Moreover, neuroimaging shows an increased amygdala volume and hyperactivity in the general limbic region, an area that has been associated with fear response (37). Other studies have detected a hypertrophy in the amygdala after laboratory animals are subjected to stress (38).

The second theory is based on neurotransmitters. The first neurotransmitter pathway that has been linked to anxiety is the dysregulation of GABA inhibitory neurotransmitters. GABA, or γ-aminobutyric acid, is the principal inhibitory neurotransmitter in the central nervous system, and its main role is decreasing neuronal excitability. This theory, much as the ones we discussed with depression, is inferred from anxiolytic treatment response.

Another theory involves CCK-4, or Cholecystokinin Tetrapeptide, a neurotransmitter with affinity with the CCK-B (Cholecystokinin-B) receptor in the central nervous system.

Intravenous administration of CCK-4 creates panic attacks in patients already diagnosed with anxiety disorders and in healthy participants as well, although in higher doses (39). Furthermore, a possible reduction of CCK-B by genetic deletion of TRPC4 or TRPC5 proteins reduces anxiety in mice (40).

Finally, around 32% of GAD cases stem from genetic vulnerability; the other 68% could be explained by an "environment specific to the individual" (38). However, identifying the specific genetic components of anxiety has been challenging and no definitive answer is available at this time (41).

II. Psychedelics

A. An introduction into psychedelics

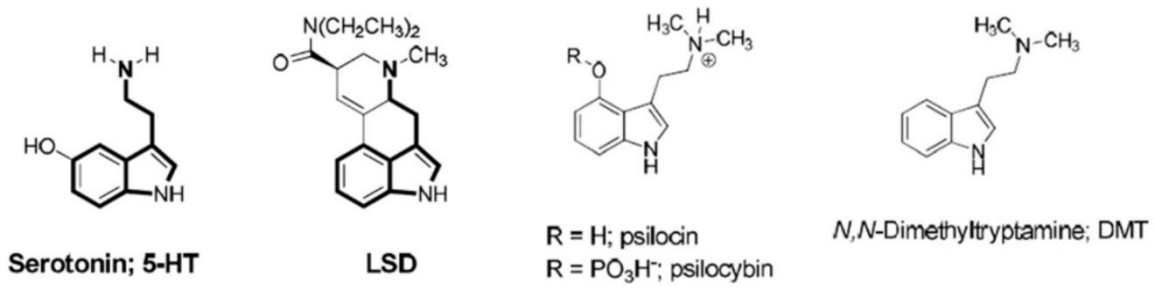

Figure 1: Extracted from *Fig. 1. Chemical structures of serotonin and LSD* and *Fig. 2. Chemical structures of classic psychadelics mescaline, psilocybin, and DMT.* (9)

These substances, also called serotonergic hallucinogens, create their mind-altering effects from partial agonism to the $5HT_{2A}$ receptor (42) due to their similar structure to the neurotransmitter serotonin (5-HT) (9) (Figure 1). This has been demonstrated through administration of ketanserin, a selective $5\text{-}HT_{2A}$ antagonist, before psychedelic dosing in human and animal studies: when ketanserin is administered, it blocks the hallucinogenic properties of psychedelics, including vision hallucinations and head twitches in mice (9,43).

Although there is recorded use of psilocybin, ayahuasca and other psychedelic substances dating so far back in time some consider them "the oldest class of psychopharmacological agents known to man" (9), the discovery of LSD expanded recreational psychedelic use into the mainstream. The use of these substances by so-called hippies while demonstrating against the Vietnam War and the fear induced by reports of drug-induced insanity contributed to the decision to place these drugs in the Schedule I category (9).

However, it has been demonstrated that these substances are not addictive and relatively safe. As a matter of fact, in 2010, more than 30 million people living in the US had used psychedelics and no correlating mental health problems were found (44).

On the contrary, psychedelic use has been linked to increased mental health and anxiolytic and antidepressant effects.

B. Ayahuasca

1. The pharmacology of ayahuasca

Ayahuasca is a traditional Amazonian decoction made from the bark of the *Banisteriopsis caapi* vine and leaves of the *Psychotria viridis* bush.

Psychotria viridis is a plant from the *Rubiaceae* family. It contains dimethyltryptamine (DMT), a hallucinogenic alkaloid. *Banisteriopsis caapi* is a South American giant vine from the *Malpighiaceae* family. It contains three alkaloids (harmine, harmaline and tetrahydroharmine) from the beta-carboline class that can act as monoamine oxidase inhibitors.

DMT has long been studied as a hallucinogenic, the main effect of which is visual hallucinations. It is physiologically degraded by MAO, more specifically, MAO-B. DMT is consequently not orally active (45).

The alkaloids present in *B. caapi* have a tryciclic β-carboline structure. Both harmine and harmaline act as selective and reversible MAOI-As, while tetrahydroharmine (THH), although also inhibiting MAO, is active mainly from serotonin uptake inhibition (46).

It has been theorised that this MAO inhibition is what permits DMT to reach the central nervous system when ayahuasca is consumed, as it would otherwise be degraded peripherally by MAO-B (45). However, this MAO inhibition is peripheral and short-lived, which means that only about 15% of DMT reaches the central nervous system (45).

DMT is a serotonergic neurotransmitter with a similar structure to serotonin. It is a 5-HT_{2A} and 5-HT_{1A} agonist, and its interaction with 5-HT_{2A} increases neural firing through excitatory post-synaptic currents and stimulates immediate early gene expression; a gene that increases BDNF expression, and consequently, promotes brain plasticity (45). Additionally, DMT has affinity for the SR1 receptor (the intracellular σ-one receptor), an endoplasmic reticulum-associated receptor that also promotes neural plasticity (45).

Furthermore, DMT has been proven to be an agonist to the TAAR (trace amine associated receptor), which could increase DMT levels to ones that would be significant for the SR1 receptor. Finally, DMT is a substate of the vesicular monoamine and serotonin transporter, which would keep its levels in the central nervous system at a safe threshold (45). Finally, some MAO-independent biotransformation routes for DMT have been found, limiting even further the possibility of adverse reactions (47).

2. *Ayahuasca and neuroimaging*

When neuroimaging is done to healthy volunteers after ayahuasca intake, studies have reported a broad-band decrease in spontaneous brain electrical activity, specifically, in α-band oscillations. These were reported to correlate inversely with visual effects, and both the correlation and the visual effects could be blocked by pre-treatment with ketanserin, a 5-HT_{2A} antagonist (48,49). Furthermore, an excitatory effect on the cerebral cortex was found, as well as changes in the posterior sensory processing regions, the frontal areas regulating emotional processing and cognitive control and memory processing. Contrary to what was expected, no changes were reported in any visual or auditory areas (45).

Finally, ayahuasca has been reported to modify the flux of information in the brain. Alonso *et al*., in 2015, reported a modification of the normal hierarchical structure regulating the brains' flow of information (47).

As for studies investigating long-term use of ayahuasca, they reported a decrease in cortical thickness in the posterior cingulate cortex, a region that has been found to be thickened in the event of depression (45).

3. *Acute and long-term effects of ayahuasca*

In a clinical study setting, active doses of ayahuasca range from 0.6 to 1 mg DMT/kg body weight (45,50).

When ayahuasca is consumed, there is usually about 15 to 30 minutes of lag-time. After that, stomach pains and a change in skin sensitivity have been reported by volunteers participating in a study (51). The visual imagery starts at about 45 minutes to an hour after the first administration. These images are compared to dreams in the way they feel, and their containing scenes featuring people and places the participant knows. These 'dreams' usually disappear if the participants open their eyes, and the participants are aware that the visuals are drug-induced. Moreover, participants report an increase in thought speed.

These effects reach their maximum around one and a half to two hours after administration, and participants return to their baseline after four to six hours (51). One important factor of ayahuasca experiences is the fact that the visual imagery is centred around previous experiences, and faster thought processing facilitates new associations, sometimes triggering intense emotions or reflections on personal feelings (45). Reports of an ayahuasca 'afterglow' are also important to consider.

This ‘afterglow’ is described as “increased positive mood experienced in ayahuasca users for up to 2 months after use” (52). This is usually ascribed to an increase in mindfulness-related capabilities to ayahuasca users.

Mindfulness is described as “paying attention in a particular way: on purpose, in the present moment, and non-judgmentally” (53). Mindfulness can be tracked using the Five Facets Mindfulness Questionnaire, which encompasses all five facets of mindfulness: observing, describing, acting with awareness, non-judging of inner experience and non-reactivity to inner experience (54). Mindfulness has been proven efficacious in treating both depression and anxiety (55), and the psychiatric population has been found to score lower on the mindfulness scale (45).

Ayahuasca also has been described to increase the ‘decentering ability’, also called ‘defusion’. This has been described as “the ability to observe one’s own thoughts and feelings in a detached manner” (45) and it could enhance acceptance during the introspective state, aiding trauma recovery. Dominguez-Clavé *et al.* (45) concluded that the antidepressant and anxiolytic properties of ayahuasca could be brought by its mindfulness-enhancing properties, that last up to two months after a single dose (56).

All of this results in a weakening of normal thought limitations and a strengthening of memory and emotional processing through the dream-like state, which could be a factor in its antidepressant and anxiolytic properties.

Physiologically, ayahuasca has sympathomimetic effects, increasing norepinephrine release (50) and creating mydriasis and an increase in cortisol and prolactin production (45). However, no changes in heart rate, very moderate increases in systolic and diastolic blood pressure and little side effects mean that ayahuasca is usually considered safe (45). Furthermore, the main side effect, vomiting, is sometimes seen by ayahuasca users as a “beneficial ‘purging’” (45).

Apart from vomiting, some volunteers have reported anxiety reactions and even transient dissociative episodes, but receiving verbal support seems to mitigate them (51). Psychotic episodes related to ayahuasca intake have been reported, although in small sample sizes, but it appears that previous screening for psychiatric disorders minimizes the risk of a psychotic episode (57).

4. Clinical evidence for the use of ayahuasca in mood disorders

The past twenty years have seen a trickle of clinical trials using ayahuasca to treat anxiety and depression.

Barbosa *et al.*, in 2005, reported a decrease in anxiety and depression symptoms after a single dose of ayahuasca in 19 first time users, and behavioural changes in all 28 study participants (58). However, they did not report the composition of the ayahuasca brews they

used in the study, as it isn't a standardised concoction. All other studies reported brew composition through spectrophotometer results.

Osorio *et al*., in 2015, reported up to 82% reduction in depressive scores for patients with acute depression after a single dose of ayahuasca (59) and Sanches *et al*., in 2016, observed decreases in depression scales to psychiatric patients after a single dose (60).

Additionally, observational studies of ayahuasca users report a general improvement of mood and anxiety disorders (61). However, these trials were open-labelled and not randomized, so the antidepressant effects that were observed could not be attributed to ayahuasca use. Because of all of this, and the fact that these trials used small sample sizes, they could only conclude that ayahuasca held potential as an antidepressant and anxiolytic substance.

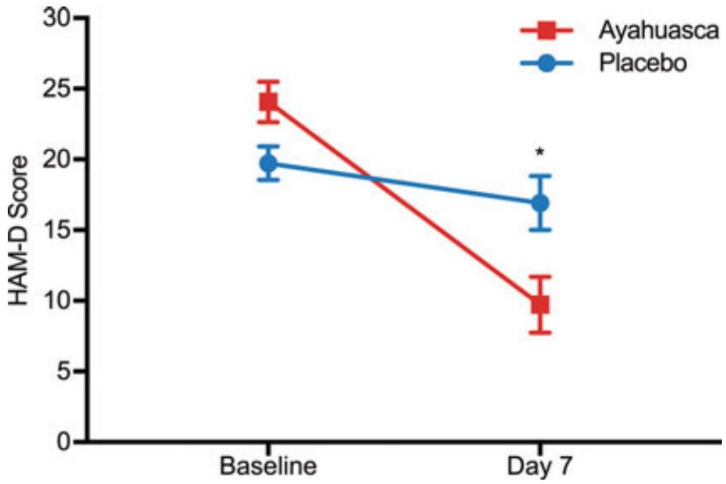

Figure 2: *HAM-D scores at baseline and seven days after dosing. Statistical analysis shows a significant difference between ayahuasca (squares) and placebo (circles) seven days after dosing (p = 0.019). Between-group effect size is high (Cohen's d = 0.98). Values are (mean ± S.E.M.). HAM-D scores: mild depression (8–16), moderate (17–23), severe (⩾24).* (62)

However, in 2019, Palhano-Fontes *et al.* conducted the first randomized controlled trial involving ayahuasca (62). They studied 29 patients diagnosed with treatment-resistant depression, to whom they administered a single dose of either ayahuasca or placebo. The changes were measured on the Hamilton Depression Rating scale and the Montgomery-Åsberg Depression Rating Scale (MADRS), a reliable and valid diagnostic tool for depression (63). The sample size was quite small, but they observed "significant antidepressant effects" (62) (Figure 2).

C. Psilocybin

1. The pharmacology of psilocybin

Psilocybin is a secondary metabolite found in more than two hundred species of basidiomycetes, a division of fungi (64). Secondary metabolites, organic compounds produced by fungi, plants, and bacteria, have been looked upon as a source of novel therapies (64). Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a tryptamine that produces a psychedelic experience, creating changes in perceptions in a dream-like state (65).

Psilocybin mushrooms, called *teonanacatl*, 'god's flesh' in South America (9), are used, much like ayahuasca, in a sacramental context, earning the label of "sacred mushrooms of Mesoamerica" (64), or, more recently, 'magic mushrooms'. These contain between 0,1% and 2% psilocybin by dry weight, depending on the specific species (64).

Psilocybin is rapidly dephosphorylated by an alkaline phosphatase in the intestinal mucosa (66) and metabolized into psilocin. This change is so rapid that some classify psilocybin as a prodrug (66).

Psilocin is a serotonin transporter inhibitor, a 5-HT_{2A} receptor partial agonist and, at lower affinity, a 5-HT_{2C} receptor, a 5-HT_{1A} receptor and a 5-HT1B receptor partial agonist (67). Its psychedelic properties are dose-dependent and correlate in intensity with 5-HT_{2A} receptor occupancy and levels of psilocin in plasma (68).

Psilocybin has been found to block the activity of inflammatory cytokines, specifically TNF-α, a cytokine that is reportedly increased in depressed patients. This would be in line with a theory according to which, in the brain, a plasminogen activator and inhibitor imbalance would favour the inhibitor, resulting in a neuroinflammation that would be the cause of depression (69).

2. Neuroimaging and psilocybin

As far as how psylocibin impacts brain mechanisms, Carhart-Harris *et al.*, in 2017 (70) observed, through an fMRI (functional Magnetic Resonance Imaging) machine, the before and after on psilocybin treatment for treatment-resistant depression. They reported reduced cerebral blood flow in the temporal lobes, including the amygdala, which were accompanied by a decrease in depressive symptoms. They also observed an increase in RSFC (resting-state functional connectivity) in the default mode network post treatment, although it decreased significantly while still under the effects of psilocybin (70). Increased RSFC in the default-

mode network has been linked to depression, specifically to depressive rumination (71). However, Carhart-Harris *et al*. argued that the increase seen post-treatment was more likely to be related to a normalization of RSFC to the levels of a healthy brain than their own usual levels, as depression symptoms were decreased in all participants of the study one week post-treatment (70).

Mertens *et al*., in 2020, observed decreased amygdala connectivity after psilocybin treatment correlating to decreased rumination (72), thus strengthening the hypothesis that psychedelic-induced decreased amygdala functional connectivity is linked to decreased depression. However, no connections between amygdala functional connectivity and anxiety have been found (72).

This decrease in cerebral brain flow in the temporal lobes and the decrease of RSFC in the default mode network was also observed in healthy volunteers in an older trial (73).

3. Acute and long-term effects of psilocybin

Psilocybin doses that create a psychedelic effect range from 0,3 to 0,6mg/kg (67) and the effects last between 3 to 6 hours (67), starting usually 20 to 40 minutes after the administration and peaking at 60 to 90 minutes (74).

Griffiths *et al*., in 2011 (75), developed a double-blind study where healthy participants were administered different oral doses of psilocybin (0, 5, 10, 20 and 30 mg/70 kg) in a randomized order. Firstly, they catalogued acute symptoms. The positive symptoms were perceptual changes (visual illusions, synesthesias…), labile moods (joy, feelings of transcendence…), cognitive changes (gaining insight or meaning) and mystical experiences, which we will discuss later. However, some participants also experienced negative symptoms, including fear and anxiety, delusions, and paranoid thinking.

The main adverse effects reported after psilocybin administration are blood pressure increase, usually non-clinically significant elevations, headaches, nausea or vomiting and anxiety. Some trial participants have experienced physical discomfort and some psychotic-like symptoms (66).

Furthermore, Griffiths *et al*. observed that participants that felt most anxiety experienced weaker mystical experiences (75).

Mystical experiences have been described for centuries, and while some are intrinsically religious, it has been hypothesised that all mystical experiences have a “common core” that each individual’s reality and culture fills with theological interpretations (76). Mystical experiences are quantified using the Pahnke-Richards Mystical Experience Questionnaire that covers four factors: mystical (including unity and sacredness, among others), positive

mood, transcendence of time and space and ineffability (76). These mystical experiences have a positive impact on patients suffering from anxiety and depression, which they described as meaningful, and patients having experienced a 'complete' mystical experience showed increased life satisfaction and mood lasting 14 months (75).

Some studies have described the acute effect of psilocybin to create "oceanic boundlessness" and auditory alterations (74).

Griffiths *et al*. (75) also undertook follow-ups one month and fourteen months after the sessions. These concluded that most participants had increased positive attitudes towards life and self, positive mood and behaviour changes and increased spirituality, all dose dependent. Personal meaningfulness also rose more for people given psilocybin, and most for those with higher doses. Finally, most participants that had been given the highest dose described the experience as the "single most spiritually significant" of their lives (75).

At the fourteen-month follow-up, they detected no decrease in well-being or life satisfaction, on the contrary, around 80% of participants rated either the 20mg/70kg or the 30mg/70kg dose as having "increased well-being/life satisfaction (moderately or very much)".

4. Clinical evidence for the use of psilocybin in mood disorders

Watts *et al*., in 2017 (77), carried out an open-labelled trial where twenty patients suffering from treatment-resistant depression were interviewed about their psilocybin experience in a previous trial, Carhart-Harris *et al*., 2016 (78). The patients described depression as a form of disconnection, a feeling that has been echoed a few times in the last few years, most notably by Johann Hari's book, *Lost Connections: Uncovering the Real Causes of Depression – And the Unexpected Solutions* (79).

The study participants recounted this disconnection as a disconnection from others, from the senses, from self and from the world. After the psilocybin experience, they described it as bringing connection and mental clarity. They felt an improvement in sensory capacities lasting well beyond the session and an increase in self-worth. Participants said that they began engaging in past and new activities and started having new values and perspectives. Overall, they felt a connection to others and the world (77).

Study participants also described depression as an "avoidance of emotion". They felt that psilocybin created a space where they were able to surrender to their emotions and confront their trauma, finally accepting their emotions (77). All of these changes had persisted after a period of six months, well beyond the acute symptoms of psilocybin (77).

A few randomized controlled trials have been published in the last few years studying the treatment of anxiety and depression with psilocybin. Notably, these trials are centred on patients suffering from anxiety and depression related to life-threatening cancer.

Grob *et al*., in 2011 (80), and Ross *et al*., in 2016 (81), conducted crossover trials using psilocybin and niacin as an active placebo.

The first found BDI scores to drop around 30% after psilocybin administration, but, most importantly, this drop was sustained and still significant at the 6-months follow-up. STAI score decrease was also found to be substantial and still significant after 1 and 3 months. The participants described oceanic boundlessness and a "visual destructuralization of dimensions" (80), while some also felt anxious ego dissolution and auditory alterations, but no participant felt any significant adverse psychological effects. They concluded that a hallucinogen treatment model was feasible for patients suffering from advanced-stage cancer and anxiety (80).

Ross *et al*. (81) utilized a slightly higher dose of psilocybin to the same niacin dose, and combined psilocybin or placebo sessions with psychotherapy. They found immediate, substantial, and sustained decreases in anxiety and depression up to 26 weeks (6 months) after a single dose of psilocybin. Instead of a decrease in death anxiety, participants described an improvement in attitudes and adaptation towards death (81).

However, both studies presented a small sample size (n=12 and n=29) and difficulty maintaining blinding, as it was very easy to distinguish between psylocibin and placebo, for both the participants and the study monitors.

Griffiths *et al*., in 2016 (82), while studying the effects of psilocybin on cancer patients, maintained double-blindness utilizing a very low dose of psilocybin (1 or 3 mg/70 kg) to act as a placebo, and a high dose (22 or 30 mg/70 kg) of psilocybin to act as the active drug. Furthermore, they recruited community observers (family and friends of the participants) to rate behavioural changes. They observed increased quality of life, increased life meaning, death acceptance and optimism after a single dose of psilocybin lasting up to 6 months in 80% of participants (82).

Davis *et al*., in 2020 (83), studied psilocybin and therapy treatment for Major Depressive Disorder. In this randomized controlled trial, two groups of patients received a psilocybin dose either immediately after the beginning of the study or 8 weeks later. This delay created a control accounting for the effects of having been accepted into the trial, but failed to control for expectancy effects, for example, as they did not use an active o inactive placebo. They found significant antidepressant effects lasting up to 4 weeks in 74% of participants (83).

Separate from these trials, open-label trials have also been conducted in the past few years that reach the same conclusions: psilocybin reduces anxiety and depression up to a few

weeks after a single dose is administered, and some even achieved complete remission after three months (78,84).

Following this, it has been hypothesised that psilocybin could have antidepressant effects through mystical experiences that facilitate emotional processing (72).

D. LSD

Lysergic acid diethylamide, commonly called LSD, is a semisynthetic psychedelic compound, and the last substance we will cover in this review.

LSD was first synthesised by Albert Hoffman, a Swiss chemist, in 1938, while studying ergot derivates and their potential therapeutic uses at Sandoz Laboratories. After not sparking a lot of interest, the project was benched until April 1943 (85).

Hoffman, having involuntarily ingested LSD a few days earlier and experienced some psychedelic effects, ingested 0,25mg of LSD on April 19th, 1943, and experienced very strong psychedelic effects. During the following years, experiments involving Hoffman's colleagues at Sandoz Laboratories were performed, and, in 1947, the first scientific study involving LSD was completed (85).

Sandoz then made LSD available to research laboratories under the name 'Delysid'. The investigation groups working with LSD took two different approaches: the first, called 'psycholitic' approach, involved administering multiple low doses of LSD as an aid to therapy. The second, called 'psychedelic', involved creating a life-changing experience using a single dose of LSD, usually administered to volunteers suffering from addiction and personality disorders (85). Other studies involved administering LSD to patients suffering from cancer, where researchers observed that LSD produced not only pain relief, but a view change regarding their illness and situation (86).

After LSD discovery, inquiries into the structure of serotonin accelerated, and some credit its discovery with setting in motion the field of serotonergic neuroscience (9).

Before the FDA placed LSD in the Schedule I list in 1970, around a thousand clinical papers discussing LSD had been published, involving up to 40.000 patients (9). After, decades passed with barely any publications on the subject, until the 1990's, when interest into LSD resurfaced (87).

1. The pharmacology of LSD

LSD is a tryptamine that binds to 5-HT_{1A}, $5HT_{2A}$ and $5HT_{2C}$ receptors, as well as dopamine D_2 and adrenergic α_2 receptors.

LSD is usually administered orally. Its psychedelic effects start around 30 to 60 minutes post administration, peak at around two hours post administration and the effects stay high another three to five hours lasting up to 12 hours (88). However, LSD can also be administered intravenously, the effects then start 15 to 30 minutes after administration and peak 45 to 90 minutes after dosing (89).

LSD can create tolerance. After a 2 to 3 days of daily moderate doses, a tolerance is developed, and the same doses produce a decreased psychological effect. However, this tolerance disappears after 2 to 3 days of non-administration, or placebo (90).

Like other serotonergic psychedelics, LSD activates frontal cortex glutamate transmission, which could have modulatory effects of subcortical areas, finally modifying gating functions in sensory and cognitive processes (87). However, LSD binds $5HT_{2A}$ receptors more potently that other serotonergic psychedelics, a possible explanation as to LSD' stronger hallucinatory properties. Besides, LSD has also been proven to bind 5-HT_1 receptors more potently than other serotonergic psychedelics, but no studies to this day have been conducted to ascertain the physiological function of 5-HT_1 receptors (87).

Moreover, LSD presents $TAAR_1$ (trace amine-associate receptor 1) agonism, a receptor that has been evidenced to have antidepressant, antipsychotic and anti-addictive properties (91). Furthermore, LSD has been proven to improve neuroplasticity following the same pathways as ayahuasca (91).

Finally, it has been hypothesised that LSD blocks inflammation by activating 5-HT_{2A} receptors, as these block TNF-α modulated inflammation *in vivo* (92).

2. LSD and neuroimaging

As far as LSD effects on the brain, it has been evidenced to diminish firings of dopaminergic neurons in the ventral tegmental area, the main source of dopaminergic neurons, and diminish serotonin transmission in the dorsal raphe nucleus through 5-HT_{2A} and D_2 receptors (93). These functions are dose-dependent, the second appearing at low doses and the first at higher doses, indicating that LSD at high doses affects dopaminergic mesolimbic neuronal activity in a multi-receptor mechanism, as D_2, 5-HT_{1A} and $TAAR_1$ receptor antagonists prevent these actions (93).

In 2018, Müller *et al*. performed an double blind randomized clinical trial in which they administered 100µg of LSD and placebo to healthy participants and measured their brain activity through functional magnetic resonance imaging (94). They observed a decrease in functional connectivity *within* visual, auditory, and sensorimotor network, as well as the default mode network (94). A decreased coactivation within the default mode network has been linked to ego dissolution (95). However, analogous modifications in *within* network connectivity were seen using sertraline, which could indicate that these variations are not particular of psychedelics, but perhaps of the serotonergic system (94)

However, they also observed increased *between* network connectivity, specifically in the subcortical and cortical hub structures, in the thalamus and striatum particularly (94). Hub structures have been linked to depression: some posit that hub structures are altered in depression and that, through its anti-inflammatory action, LSD 'resets' these regions (9).

This increase in *between* network connectivity relates to findings about an increased global connectivity in the brain after the administration of LSD (96). These findings have led to the hypothesis that LSD induces a collapse of normal brain hierarchies, connecting sensory and association regions of the brain, which would be a cause of ego dissolution (96).

Ego-dissolution is a type of self-awareness where the notion of the self as individual and apart from the rest of the world lessens or even disappears (97). It is sometimes seen as a positive, enhancing the union of the individual to the world and others, and sometimes as negative (anxious ego-dissolution), where one would feel a loss of the self (98).

3. Acute and long-term effects of LSD

When receiving a dose of LSD in a clinical trial setting, participants relay auditory alterations, a feeling of well-being, visionary restructuralization (complex imagery coupled with audio-visual synaesthesia during which visions change meanings) and oceanic boundlessness linked to depersonalization and derealization creating feelings of unity (88). Although these acute effects are very similar to those of other psychedelics, as it has been noted earlier that LSD perceptual alterations are stronger than those of other psychedelics.

Furthermore, it has been noted that LSD creates an empathogenic mood closer to the one experienced while administering MDMA (3,4-Methylenedioxymethamphetamine) (88). This empathogenic mood brings the participants feelings of closeness, openness and trust (88).

Physiologically, LSD induces an increase in blood pressure, heart rate and body temperature, as well as a plasma concentration increase in cortisol, prolactin, oxytocin and epinephrin (88). Oxytocin is the neuropeptide that has been linked to the empathogenic effects of MDMA, and it has been hypothesized to render the same effect in LSD (99).

LSD has also been reported to amplify emotional response to music, an effect that has been looked into to be used in therapeutic settings, as it has been noted that the combination of music and LSD might increase mystical experiences (100).

However, LSD also created anxiety through anxious ego-dissolution and disembodiment (88,95), impaired cognition, cognitive disorganisation, paranoia and fears of losing control, delusional thinking and flashbacks (95).

Flashbacks, or Hallucinogen Persisting Perception Disorder (HPPD), is an uncommon and poorly understood disorder in which individuals experience central nervous system malfunctions for up to a year after a single dose of a psychedelic drugs, experiencing visual distortions and hallucinations without being under the influence of a psychedelic drug (101). This disorder is more commonly triggered in patients already diagnosed with a psychological disorder such as schizophrenia, or a family history of such psychological disorders, but can appear in healthy patients as well (101).

Furthermore, Carhart-Harris *et al*., in 2016, administered LSD intravenously to 20 healthy volunteers and measured its subjective effects using the Altered State of Consciousness (ASC) and the Psychotomimetic States Inventory (PSI) questionnaires, the second of which is used to rate psychosis-like events (95). Although they detected very high PSI scores, leading them to hypothesise that the participants' experience was a negative one, most of the volunteers acknowledged that, although difficult in stages, the experience had been mostly pleasant and more positive than negative. The researchers theorised that the PSI scores might have been higher than expected because the participants spent a portion of their LSD experience inside an MRI machine, but still found it paradoxical.

Furthermore, at a two-week follow-up, optimism and openness in most participants had increased and they felt heightened psychological wellbeing (95). This is supported by another study, Schmid *et al*., 2018, that found improved mental wellbeing up to a year after a single dose of LSD (102).

Carhart-Harris *et al*. hypothesised that while under acute psychedelic effects, an unconstrained thought dynamic, consistent of ego dissolution and disembodiment among others, provokes distress; but in the long term, these modified brain pathways increase wellbeing and optimism (95).

This neurological state, also called 'entropic brain', seems to be brought by heightened $5HT_{2A}$ receptor stimulation in certain areas of the brain (103).

4. Clinical evidence for the use of LSD in mood disorders

The only randomized controlled trial that has been concluded to date with patients suffering from mood disorders is the one performed by Gasser *et al*. in 2014. They administered either 200µg or 20µg of LSD (the second acting as an active placebo) during psychotherapy sessions to 12 patients suffering from anxiety related to life-threatening diseases. They saw reductions in trait anxiety and state anxiety for up to a year post-treatment with no acute or lasting adverse effects starting at a day post administration (104).

After this successful trial, the Swiss government approved the compassionate use of LSD in a case-by-case basis. As of 2017, 10 patients had been treated with LSD by Dr Peter Gasser in a group setting (105).

Other non-completed clinical studies have been investigating the effects of LSD on anxiety with volunteers suffering from or not a life-threatening illness (ClinicalTrials.gov identifier 03153579).

DISCUSSION

The current scientific evidence, although limited, is promising and supports further investigation into the therapeutic effects of psychedelics for the treatment of anxiety and depression.

Further societal and governmental acceptance of psychedelics in therapeutic settings, such as the FDA's "breakthrough therapy designation" of psilocybin (106), are key to allow clinical trials involving psychedelics to multiply until solid evidence is achieved. However, if psychedelic drugs remain illegal for the public and interest in them grows once again, there is danger in unclear compositions and undiagnosed psychiatric conditions, as it could trigger worse adverse effects and even flashbacks (101).

The common adverse effects of psychedelic dosing (vomiting, anxiety…) as well as the more uncommon but increasingly dangerous such as flashbacks (101) are hurdles in its clinical setting application. Furthermore, their hallucinogenic properties, while sought after by many, are not the most agreeable for the general psychiatric population, and thus are not yet suitable for general clinical setting.

Other hurdles to overcome are the methodological aspects of clinical trials involving psychedelics; mainly the low number of participants, the failure of more long-term follow-ups and the difficulty in blinding the process.

One aspect of psychedelic research that must be further investigated is the mechanisms of their anxiolytic and antidepressant effects. One theory that stands out is the one involving neuroplasticity through BDNF stimulation (107,108) (Figure 3). As neuroplasticity has also

been linked to modern antidepressant drugs (24), it would be plausible to think that psychedelic drugs act through the same means. However, as psychedelic drugs do not present a delayed onset of pharmacological action similar to that of modern antidepressants, other modes of action need to be considered.

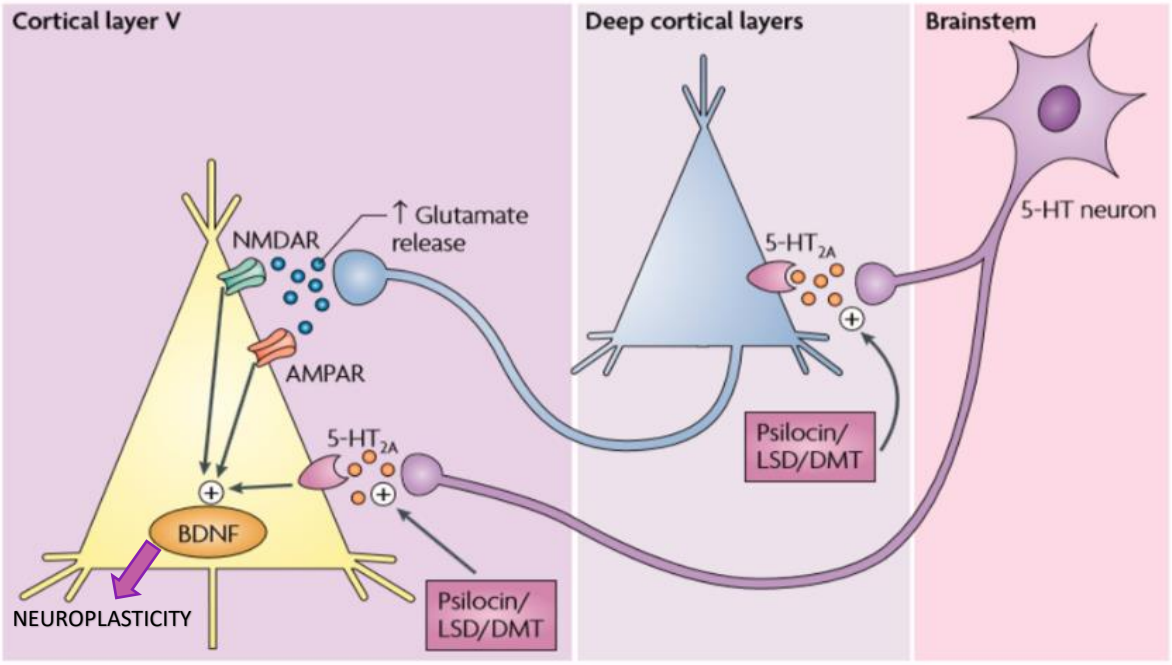

Figure 3: Modified from *Glutamatergic synaptic activity is modulated by specific5- HT2A antagonists such as AMPA (α-amino-3-hydroxyl-5-methyl-4- isoxazole-propionic acid), positive allosteric modulators of metabo- tropic glutamate receptor 2 (mGluR2) and selective antagonists of the NR2b subunit of NMDA receptors. (Reprinted with permission from Springer Nature: Nature Reviews Neuroscience, 2010)* (107)

Although it is also plausible to assume that the hallucinogenic properties of psychedelics are the main cause of their anxiolytic and antidepressant functions, newer studies observing the effects of micro-dosing psychedelics (administering psychedelics, usually LSD and psilocybin, at a dose where hallucinogenic effects are barely felt) tell the opposite. In these, improvements in mood and renewed connections are observed, very similar to results using full doses of psychedelics (109).

All things considered, the possibility of an effective and safe therapy consisting of a single dose every few weeks or even months, especially for patients also suffering from life-threatening illnesses, is very promising, and current evidence invites further research.

Precedent from Doctor P. Gasser in utilizing LSD therapy in a clinical setting for compassionate use (105) invites further approvals on similar grounds. It is my opinion that the evidence is compelling enough to permit a small scale and case-to-case approval of psychedelic therapy. I believe that at present the approval should only be on grounds of compassionate use, but that as further evidence is attained, approval should not stay limited to compassionate use. In my point of view, these therapies, if proven safe, could

revolutionise anxiety and depression treatment and ameliorate the quality of life for many suffering from these mood disorders.

CONCLUSIONS

1. Depression and anxiety are widespread mood disorders, the treatment of which is not effective for all patients, has a delayed onset and creates many adverse effects.
2. The psychedelic substances studied in this review, ayahuasca, psilocybin and LSD, have demonstrated anxiolytic and antidepressant effects lasting for weeks after a single dose.
3. Although the evidence is limited and needs further study, it is very promising and could be approved in a case-to-case basis.

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