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REVIEW ARTICLE

NON-PHARMACOLOGICAL TREATMENT METHODS FOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW

NIEFARMAKOLOGICZNE METODY LECZENIA DLA ZABURZEŃ DEPRESYJNYCH

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ABSTRACT
Depressive disorder is a widespread psychological condition. It affects approximately 5% of adults globally. Untreated depression can compromise the quality of life in all its aspects, leading to deterioration of physical health or even suicide. Currently, the recommended treatment is pharmacological therapy, however, not all patients respond to traditional methods, and drug treatment is related to many undesirable side effects. While antidepressants remain the gold standard, non-pharmacological treatment methods are gaining popularity and recognition in Western medicine. While these methods are not always available as a substitute for pharmacotherapy, they can complement and enhance the therapeutic effects. In this paper, we will cover the newly researched, holistic methods of non-pharmacological treatment of depression, including physical exercise, dietary adjustments, psychedelics, or mindfulness, as well as the commonly accepted techniques, such as psychotherapy, electroconvulsive therapy, or deep brain stimulation. This review aims to present alternative treatments for depression and offer insight into the complex topic of improving quality of life and obtaining general well-being.

Keywords: depression, depression treatment, depressive disorder, non-pharmacological treatment of depression, depression management

STRESZCZENIE
Depresja jest szeroko rozpowszechnionym zaburzeniem psychicznym. Dotyka około 5% dorosłych na całym świecie. Nieleczona depresja może pogorszyć jakość życia we wszystkich jego aspektach, prowadząc do pogorszenia zdrowia fizycznego, a nawet samobójstwa. Obecnie zalecanym leczeniem jest terapia farmakologiczna, jednak nie wszyscy pacjenci reagują na tradycyjne metody, a leczenie farmakologiczne wiąże się z wieloma niepożądanymi skutkami. ubocznymi. Podczas gdy leki przeciwdepresyjne pozostają złotym standardem, niefarmakologiczne metody leczenia zyskują coraz większą popularność i uznanie w zachodniej medycynie.

Chociaż metody te nie zawsze są dostępne jako substytut farmakoterapii, mogą one uzupełniać i wzmacniać efekty terapeutyczne. W niniejszym artykule, omówimy nowo zbadane, holistyczne metody niefarmakologicznego leczenia depresji, w tym ćwiczenia fizyczne, dostosowanie diety, psychodeliki lub uważność, jak również powszechnie akceptowane techniki, takie jak psychoterapia, terapia elektrowstrząsowa czy głęboka stymulacja mózgu.

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Niniejszy przegląd ma na celu przedstawienie alternatywnych metod leczenia depresji i zaoferowanie wglądu w złożony temat poprawy jakości życia i uzyskania ogólnego dobrostanu.

Słowa kluczowe: depresja, leczenie depresji, zaburzenie depresyjne, niefarmakologiczne leczenie depresji, zarządzanie depresją

Introduction

Depressive disorder also known as depression is a common psychiatric disorder which includes symptoms such as low mood, loss of energy, problems with sleeping, suicidal thoughts and reluctance to perform daily activities. Depressive episodes which last for at least two weeks differ from regular mood changes or grief periods and significantly reduce the quality of life. Depression has a major influence on both personal life and work environment due to visible lack of pleasure and interest in undertaking new or familiar activities.

The factors which contribute to becoming depressed have biological, psychological and social background. Though some people for example victims of sexual abuse or people suffering a bereavement are more likely to fall into depression, it can betide anyone.

It is estimated that worldwide 3.8% of the population that is approximately 280 million people suffer from depression. There is a higher percentage of depressed women (6%) and slightly lower of depressed men (4%). Depression can ultimately lead to suicide and is responsible more than 700 000 deaths every year (Depressive Disorder (Depression), no date).

Aim

The aim of this systematic review is to explore unstandardized methods of depression treatment since 10–30% of patients are drug-resistant. Moreover, 63% of depression patients don't respond well to pharmacological treatment and the prevalence of side effects is high. This paper comprehensively analyses the approved non-pharmacological treatment methods as well as the alternative approaches as they have gained importance in terms of social and cognitive aspects.

Materials and methods

This systematic review paper was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The eligibility criteria were as follows. We included studies that investigated non-pharmacological treatments for depressive disorder, irrespective of the patients' nationality, age (adolescents, adults, elderly), or gender. Inclusion of all groups underlined the importance of assessing success rates for all non-pharmacological treatment methods mentioned as depression is a widespread disease. To ensure the review captured a broad range of approaches, studies using both human and animal models were considered. Animal studies were considered only if they were used to test the efficacy of certain non-pharmacological depression treatments. The inclusion criteria specified that only publications in English or Polish were eligible. Types of works chosen included: meta-analyses, reviews, systematic reviews, books, guidelines. Case reports were excluded from the selection criteria. Works were primarily chosen according to their title and/ or abstract. Then, an in-depth analysis of full text or certain sections was made by each member of the team. No tools were used for text screening. Initially, a 5-year publication window (2019 onwards) was applied, but due to the established nature of certain treatments (e.g., TMS, ECT), earlier studies were also included (*1967, 1977, 1985, 1995, 1997, 1998, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018*). This allowed for a comprehensive examination of both recent advancements and foundational research. Only published manuscripts were eligible for inclusion. The search strategy included

finding sources in *PubMed* and *Google Scholar*. These databases were chosen as they serve as reliable sources of medical knowledge. Additionally, a scientific journal *Psychiatria Polska* was searched through as it provides valuable knowledge in the field of psychiatry. All sources chosen provide insightful pieces of knowledge about non-pharmacological treatment methods for depressive disorder. As the scope of our systematic review is broad, many different papers researching various topics had to be used. All databases were searched manually by 5 independent people. After initial screenings, the final selection was discussed and agreed upon by the entire research team to ensure consistency and thoroughness. No software was used to aid with the data collection process.

Results

1. Approved Non-pharmacological Treatment Methods

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is widely recognized as one of the most effective treatments for psychological disorders. It is used to treat depression, schizophrenia, bipolar manic states, schizoaffective disorder, schizophreniform disorder, and catatonia. (Kellner *et al.* 2012). Its efficiency has been proven through multiple studies, (Rosenquist *et al.* 2018; Lex *et al.* 2021) and it has remained one of the most powerful tools in depression management, despite the cultural stigma. ECT originated in the 20th century and the principles of this technique have not been significantly modified since (Leiknes *et al.* 2012). ECT is based on brain stimulation treatment, achieved by applying an electrical charge through the brain to induce a seizure lasting around 30 seconds (Kirov *et al.* 2021). The procedure is conducted under controlled clinical conditions, using general anesthesia along with muscle relaxants. The recommended duration of the treatment is 6–12 sessions, scheduled two or three times per week, although these numbers can be adjusted depending on the severity of the case (Thirthalli *et al.* 2020). Research on the molecular level has provided insight into the mechanism of ECT, with the formation of several theories on the basis of action. The monoamine neurotransmitter theory suggests that ECT works by increasing the levels of serotonin and norepinephrine, which improves neurotransmission and provides an antidepressive effect (Youssef *et al.* 2018). The neuroendocrine theory entails the effect of pituitary and hypothalamic hormones, which are released upon brain stimulation. The anticonvulsant theory ties ECT effectiveness to its anticonvulsant nature. This statement could be supported by the fact that there has been noted an increase in seizure threshold and decrease in seizure duration, as the treatment progresses (Kellner *et al.* 2012). The neurotrophic theory suggests that ECT enhances neurogenesis and neurotrophic signaling in the brain, which has been proven by a recording of raised levels of neurotrophic factors, both in animals and humans (Takamiya *et al.* 2017). Despite its effectiveness, ECT does involve risk. Seizures, although controlled, can negatively impact the function of cardiovascular, pulmonary, and central nervous system, therefore testing is needed before initiating the treatment (Kellner *et al.* 2012). The most dangerous side effect of ECT is impairment of cognitive function and memory loss. These deficits can vary in severity and duration, and they can negatively impact quality of life (Lex *et al.* 2021; Kirov *et al.* 2021). Research has proven that adjusting the frequency and intensity of treatments can mitigate the negative effects (Thrithalli *et al.* 2020). While the side effects could lead to deterioration of general health, ECT is a great solution, especially for patients dealing with treatment-resistant depression. In a meta-analysis of 34 studies, the calculated response rate reached 60.5% and a remission rate of 47.8% (Van Diermen *et al.* 2018).

Psychotherapy

Psychotherapy has become the officially accepted non-pharmacological treatment for depression. It is believed that the effectiveness of psychotherapy for personality

disorders, anxiety or depression is comparable to the effect of drug treatment (Olano *et al.* 2022). The exception is severe depression, in which drug treatment in combination with psychotherapy has better results. There are many types of psychotherapy, (Wienicke *et al.* 2023) they are behavioral-cognitive, psychoanalytic, existential-humanistic, systemic and psychodynamic therapy. Each type of psychotherapy focuses on different parts of the complex picture of the patient's psychosocial and personality problems. The choice of therapy is individual, depending on the needs and preferences of the patient. Patients diagnosed with depression are most often referred to psychodynamic therapy or behavioral-cognitive therapy. Psychodynamic therapy (Pearce *et al.* 2022) is based on the principle of an interpretive and supportive continuum (Ribeiro *et al.* 2017; Porcelan and Scribner 2022). Interpretive interventions allow the patient to gain insight into his behavior and reduce the repetition of his problems. Provisional insight enhancement intervention is an interpretive intervention that makes unconscious impulses, defense mechanisms (Ribeiro *et al.* 2017) and wishes conscious. Reinforcement intervention involves strengthening abilities that are unavailable to the patient as a result of acute stress, (Porcelan and Scribner 2022) or have not been fully developed. Psychodynamic psychotherapy allows patients to better understand themselves, their behavior and emotions. As a result, patients become more aware of their actions and the decisions they make. It also affects the formation of relationships with other people. This happens thanks to the transfer of what lies in the human unconscious into consciousness. Depending on the patient's condition, a distinction is made among psychodynamic therapy, short-term therapy lasting up to 25 sessions and long-term therapy, which is better at preventing relapse. An extremely important aspect is the patient's relationship with the therapist, as this is the only way to see the unaware patient. In psychodynamic psychotherapy, an important point is the phenomenon of transference; that is, the identification of the therapist with a close person in whose life the patient had confidence. Then all gestures and words of the therapist are associated with this imagined person, which triggers various emotions in the patient. These emotions are a starting point and can lead to changes in how the patient feels about other relationships. There are many empirical studies that support the effectiveness of psychodynamic therapy (Ribeiro *et al.* 2017). A growing body of evidence shows that the positive changes achieved intensify after therapy ends. On the other hand, it is not a healing modality for everyone, (Olano and Rosenbaum 2022) as many do not improve or achieve only limited effect. Brief psychodynamic therapy is implemented when five criteria are met: limited time, limited goals, maintaining focus, high therapist involvement (Porcelan and Scribner 2022) and rapid intervention. Because of the limited therapy time, the therapist should adapt and overcome unforeseen challenges and quickly build a relationship with the patient. During the session, the therapist should take the right attitude towards therapy. It should be remembered that the patient-therapist relationship is extremely important during therapy and should be a priority during treatment. Despite the many controversies about psychodynamic therapy, (Ribeiro *et al.* 2017) its impact on the treatment of depression is growing. The effectiveness of psychodynamic therapy in the treatment of depression is comparable to that achieved in drug treatment (Olano and Rosenbaum 2022). Behavioral-cognitive therapy is the best researched therapeutic strategy for any mental disorder. It has been confirmed by a very large number of studies. The effectiveness of this type of therapy is equal or even greater compared to pharmacotherapy. It is believed to result in a more durable response compared to drug therapy (Sudak 2011; Gautam *et al.* 2020) and may protect against relapse. The therapeutic

concept of behavioral-cognitive coping with depression consists of three stages: focusing on automatic thoughts, depressogenic cognitive styles, and focusing on the way the person relates to others; and the behavioral changes necessary to enable the individual to move out of the problematic situation (Powell *et al.* 2008). An important aspect of therapy, as in psychodynamic therapy, is the relationship between patient and therapist. The therapist acts as a teacher, working together with the patient to achieve the therapy goal and functional thinking, which should result in positive reinforcement and social interactions (Powell *et al.* 2008; Sudak 2011). The facilitator aims to change behavior, which is likely to improve the patient's mood, appetite or sleep quality. Because of patients' memory problems and slowed thinking, therapy includes summarizing important points discovered during sessions. An important component of behavioral-cognitive therapy is behavioral activation (Sudak 2011). Its main goal of enabling patients to cope with negative symptoms. These strategies focus on engaging the patient, obtaining relevant information for therapy and alleviating symptoms. They are individualized (Powell *et al.* 2008) for each patient. Another benefit of behavioral activation is the restoration of the patient's correct thought patterns, which are associated with withdrawal and avoidance. Patients think that life has no meaning, they have no energy, they are afraid to take risks for fear of failure. In this case, it is very important for the therapist to instruct the patient and help him or her engage in the activity. When the patient has been given behavioral activation, the therapist emphasizes the cognitive aspect. This helps patients change the beliefs and behaviors that trigger a certain state (Sudak 2011) and identify automatic thoughts. A very important advantage of cognitive therapy is that the patient is active in his own treatment. This involves the patient finding negative thoughts on his own and seeking alternatives for them. He finds distorted perceptions and learns about the factors that contribute to the maintenance of depressive behavior (Powell *et al.* 2008). Cognitive-behavioral therapy is usually associated with 'homework', Patients are assigned tasks to complete outside of sessions. This is because the essence of learning new skills is practice and must be repeated (Chen *et al.* 2009) before they are automatically accepted. It has been proven that patients who use skills learned during therapy are less likely to relapse. About 70 percent of mental disorders already surface before the age of 25 and, if not treated effectively, can progress to a chronic state. People between the ages of 18 and 25 are much more likely to suffer from mental health disorders, as they are more likely to become addicted to psychoactive substances (Ritivo *et al.* 2021) and have suicidal thoughts. The online communication skills of adolescents have been used in treatment, where they can take classes to treat depressive disorders. A randomized controlled trial was conducted comparing behavioral-cognitive therapy combined with standard psychiatric care in adolescents taking place online versus conventional psychiatric care in adolescents aged 18–30 with diagnosed depressive disorders (Ritivo *et al.* 2021). All participants received classical psychiatric care, that is, one session per month, while participants in the experimental group received an additional intervention consisting of online software. The results obtained confirm that adolescent depression (Ritivo *et al.* 2021) can be effectively treated with online software therapy. This means that all possible and proven therapies must be used so that as many patients as possible have the opportunity to recover from depression.

Vagus nerve stimulation

Stimulation of the cervical vagus nerve to treat brain diseases is supported by both anatomical and functional traits. The vagus nerve contains both sensory afferent fibers and efferent motor fibers. The visceromotor efferent fibers originate in the dorsal motor

nucleus of the medulla, while the sensory afferent fibers terminate in the nucleus tractus solitarius (NTS), also in the medulla.

This dual structure allows vagus nerve stimulation (VNS) to impact on various regions and functions in the brain. Afferent fibers carry sensory information to the brain. They also influence brainstem nuclei and higher brain structures. Different fibers regulate autonomic functions, such as heart rate, lung function, and digestion. By these functions they indirectly affect brain activity. Therefore, stimulating the cervical vagus nerve can potentially treat neurological afflictions like epilepsy, depression, and inflammatory brain diseases by leveraging these pathways.

The afferent fibers of the vagus nerve use neurotransmitters such as substance P, calcitonin gene-related peptide and the excitatory amino acid L-glutamate. The nucleus tractus solitarius (NTS) projects to several key areas:

- Medullary motor nuclei.
- Structures in midbrain: locus coeruleus (LC), dorsal raphe nucleus (DRN), brainstem interneurons and parabrachial nucleus (PBN).
- Forebrain regions such as the hypothalamus, amygdala, bed nucleus of the stria terminalis (BNST), and insular cortex.
- What is more, nuclei like the LC and DRN project to limbic forebrain regions.

Thus, brain areas implicated in depression-related behaviors are innervated directly or indirectly, by projections from afferent vagal fibers terminating in the NTS.

The procedure of Vagus Nerve Stimulation (VNS) involves implanting a stimulation generator which is connected to bipolar electrodes. They are positioned around the left vagus nerve. Stimulation of the left vagus nerve, rather than the right, is preferred because of the less impact on heart rate. This is used for treating conditions like treatment-resistant depression (TRD) or epilepsy. The left vagus nerve innervates the atrioventricular node (AV). In contrast, the right vagus nerve innervates the sinoatrial (SA) node, which has a more significant effect on heart rate. Stimulation of the vagus nerves affects heart rate according to these specific innervations. The bipolar stimulating electrode contains the cathode at the proximal lead and the anode at the distal lead. This type of arrangement simplifies action potential propagation towards the central nervous system by creating an anodal block at the distal lead.

In 2000, Elger *et al.* were the firsts who observed improvement of mood in patients with epilepsy. It was irrespective of their seizure reduction. This study employed a double-blind, randomized comparison to measure the effects of various VNS doses without any control group (sham stimulation). Despite the fact that the high doses were less tolerated, 70% to 75% of patients in this group reached their assigned dose. Comparable efficacy was noted across all three dose groups. Following a 22-week treatment period, response rates ranged from 10% to 20% in the low-dose group and 19% to 31% in the high-dose group. Continued behavioral enhancement was observed over time, with 25% of non-responders at 22 weeks exhibiting a response at 50 weeks. Notably, responders at 22 weeks, particularly those receiving medium or high doses, sustained their response up to 50 weeks. The low-strength/high-frequency group demonstrated superior outcomes. Additional prospective studies are warranted, especially because of the evidence suggesting frequency-dependent effects of VNS in patients. The results can be provided by functional magnetic resonance imaging (fMRI) findings (Carreno and Frazer 2017).

Single clinical observations of improved mood in patients with epilepsy, even in the absence of better seizure control after VNS implantation, led to a pilot prospective study of the effect of VNS on mood in epilepsy patients treated with a VNS device or antiepileptic drugs. In the VNS group, there was a significant improvement in mood at three months that appeared independent of any improvement in seizure control, suggesting that VNS had a distinct effect on depressive symptoms. The same finding was reported independently in a European study conducted

around the same time in a group of patients with epilepsy (n = 11) with mild depression (O'Reardon *et al.* 2006).

However, despite promising efficacy in treating depression, the surgical risks, high costs of the procedure and potential side effects make it less attractive and restrict access. (Ventureyra 2000; Fitzgerald 2013). To overcome these barriers to the use of invasive VNS (iVNS), a non-invasive method of transcutaneous vagus nerve stimulation (taVNS) has been developed that is attracting more and more attention.

taVNS

Transcutaneous auricular vagus nerve stimulation (taVNS) by emphasizing its anatomical and functional impacts on the brain can be used as a therapy for depression. The research which was made by Peuker and Filler (Peuker and Filler 2002) identified that specific areas of the ear, such as the shells and tragus, are innervated by the auricular branch of the vagus nerve (ABVN).

This branch has significant neural projections to the solitary tract nucleus, which connects to extensive regions of the brain that are involved in depression (Badran *et al.* 2018; Butt *et al.* 2020).

Notably, taVNS has been shown to influence these brain regions similarly to invasive vagus nerve stimulation (iVNS).

Research indicates that taVNS can modulate activity in areas such as the orbitofrontal cortex, anterior cingulate cortex (ACC), dorsolateral prefrontal cortex, superior and medial frontal cortex, temporal cortex, parietal area, hemi frontal nucleus, and amygdala. These regions play essential roles in mood regulation and they are involved in onset of depression (Rush *et al.* 2005; Conway *et al.* 2006; Kraus *et al.* 2007; Dietrich *et al.* 2008; Kosel *et al.* 2011; Frangos *et al.* 2015; Kaczmarczyk *et al.* 2021).

Thus, the modulation of these brain areas through taVNS suggests its potential as a non-invasive therapeutic option for depression, offering similar benefits to classical iVNS without the need for surgical implantation.

Based on the findings of meta-analysis 'The efficacy and safety of transcutaneous auricular vagus nerve stimulation in the treatment of depressive disorder: A systematic review and meta-analysis of randomized controlled trials' it can be inferred that transcutaneous auricular vagus nerve stimulation (taVNS) has an effective and safe therapeutic effect from mild to moderate depression with comparable efficacy to antidepressants. Nevertheless, it is imperative for practitioners and healthcare providers to exercise prudence in interpreting these results, because of low to very low quality of evidence. To establish a more robust foundation for the efficacy of taVNS across different types and severity levels of depression, further multicenter double-blinded randomized controlled trials (RCTs) are warranted. These studies are essential for enhancing the quality of evidence and providing more conclusive insights into the therapeutic potential of taVNS in depression management (Tan *et al.* 2023).

Transcranial magnetic stimulation

Transcranial Magnetic Stimulation (TMS) is a non-invasive method used in neurology since 1985 (Tan *et al.* 2023). It is considered as one of the alternative methods for treatment-resistant depression (TRD) and has been approved by the Health Canada, U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) (Barker *et al.* 1985). What is unique about TMS, amongst methods such as Vagus Nerve Stimulation or Electro convulsions, is that the procedure does not interrupt with the skull structure and is performed with a full consciousness of the patient (Holtzheimer *et al.* 2014).

Over the years, several TMS methods have been developed, one example is the Repetitive TMS (rTMS). rTMS is a method that involves multiple signals over a short period of time [39]. International clinical trials proved safety and efficacy of rTMS which allowed for implementation of this method as an alternative for pharmacotherapy in TRD (George *et al.* 1995; Janicak *et al.* 2008; George *et al.* 2010).

It usually targets the Dorsolateral Prefrontal Cortex (DLPFC) of the left hemisphere (Koutsomitros *et al.* 2021) and it can depolarize or hyperpolarize certain cortical neurons (George *et al.* 1995). In the procedure, an electromagnetic coil is placed on a patient's scalp and short, but powerful (0.5–2 Tesla) magnetic fields are provided. They penetrate to the cortex inducing an electric current in neurons (Holtzheimer *et al.* 2014). Coils used in rTMS vary in shape and can be planar, helmets or figures of eight (De Risio *et al.* 2020). Additionally, various intensity and duration can be applied, but usually 10 Hz frequency is used over (Holtzheimer *et al.* 2014; Kim *et al.* 2016; Koutsomitros *et al.* 2021) weeks in daily sessions (Perera *et al.* 2016). rTMS was found to provide approximately 30–40% remission rate for TRD in various studies (Koutsomitros *et al.* 2021). Animal model studies that investigate the impact of magnetic field on neurons have shown that it can increase levels of BDNF (Janicak *et al.* 2008), influence motor learning and stimulate neural repair and axon outgrowth (Sherrard *et al.* 2018; Dufor *et al.* 2019) by the action of cryptochrome which is a magnetic sensor required in reinnervation. Meta-analysis done by Hao Li *et al.* exhibited a positive effect of rTMS on 48 adult patients with TRD (Li *et al.* 2021). rTMS was found to have an antidepressant effect also on adolescent patients. In a systematic review performed by Hett *et al.,* 14 studies were identified and all of them reported a reduction in depression scores in patients aged 14–25 (Hett *et al.* 2020).

Theta Burst Stimulation (TBS) is an alternative method based on the TMS protocol. TBS has been proposed in 2005 and it involves lower intensity of impulses and decreased stimulation time. TBS, similarly to TMS, targets the DLPFC region of the brain. There are three types of TBS: Intermittent TBS (iTBS), Continuous TBS (cTBS) and Intermediate TBS (imTBS) (Huang *et al.* 2005). Different types vary in train number and the time interval, after which the pulse is repeated. All procedures involve 600 pulses (Huang *et al.* 2005). The major difference between TMS and TBS for patients is that the deep TMS uses a 20-minute protocol, while TBS lasts for only 3 minutes (Huang *et al.* 2005). Decreasing therapy time might be more beneficial in terms of finances and time-management for patients. Amongst TBS methods, iTBS shows most promising results in decreasing depressive symptoms and suicidal thoughts in TRD (Mehta *et al.* 2022; Ekman *et al.* 2023). TBS was shown to provide higher response and remission rates compared to rTMS. A randomized controlled trial on 60 patients with depression performed by S. Bulteau *et al.* over the course of 6 months follow-up period exhibited 36.7% and 33.3% response rates, and 18.5% and 14.8% in the iTBS and 10 Hz rTMS groups respectively. However, a different study done by Spitz *et al.* has shown similar outcomes for both response and remission rates for iTBS and 10 HZ rTMS protocols (Spitz *et al.* 2022). Such findings suggest that more trials have to be performed in order to determine which method provides better response and remission rates. However, due to decreased treatment time, iTBS might be more appealing to patients. Despite promising results for TBS, this method carries a higher risk of epileptic seizures than TMS as it provides high-frequency pulse stimulation (Zhang *et al.* 2023). Other adverse effects include headaches and discomfort at the treatment site (Cristancho *et al.* 2020; Zhao *et al.* 2023). Overall, TBS protocols are safe and efficient for decreasing depressive symptoms. They are promising in terms of reducing patients' hospital exposure and lowering treatment costs. More studies are required to determine the best TBS method and to evaluate its superiority over TMS treatments.

Despite TMS being considered as safe, some adverse effects might occur. One of the most often side effects reported is transient headache which can be alleviated by simple analgesics (Janicak *et al.* 2008). Another discomfort reported after TMS sessions is the scalp pain and dizziness (Janicak *et al.* 2008; Hett *et al.* 2021). Some patients suffered from serious

adverse effects such as seizures. However, the majority of seizures were reported before the implementation of safety protocols. It is important to accurately identify seizure as it might be mistaken with myoclonic jerks. Patients that are at higher risk of TMS-related seizure are the ones suffering from neurological disorders that damage the brain structure, e.g., stroke, Alzheimer's, multiple sclerosis. Current guidelines recommend documentation of intake of drugs that can lower the seizure threshold. Other factors that lower the seizure threshold, e.g., alcohol consumption or sleep deprivation should also be considered. As stated in the US FDA's online database, only five seizure incidents were reported from 2009 to 2015. The data shows that although seizures occur, their numbers are small, even in populations at risk. Current data available, reduces the ability to accurately quantify seizure episodes, thus seizures are considered as rare (Rossi *et al.* 2021).

Deep brain stimulation

Another method of treating depression provided with biological background is deep brain stimulation (DBS) also used in treatment of diseases such as Parkinson disease, essential tremor and dystonia. Research continues to implement DBS into treatment of Alzheimer disease (Krauss *et al.* 2021).

Deep brain stimulation is an alternative for drug-resistant patients who do not respond to less invasive treatments. This neuromodulation technique supported by functional brain research and neuroimaging has both high efficiency and some possible associated risks. The mechanism of deep brain stimulation is based on a stimulator implanted in the chest skin and an electrode with its end placed in the specific brain areas. The stimulator sends impulses through the electrode and thereby disables or modifies the function of hyperactive in given disease brain areas and aligns the metabolism in relevant brain regions (Krauss *et al.* 2021). Results interpretation is possible thanks to neuroimaging (Antosik-Wójcińska *et al.* 2015).

Deep brain stimulation disables hyperactive brain areas in patients suffering from depression and increases activity in low active regions. The neurostimulation of any subcortical brain area may influence structures responsible for emotions (Krauss *et al.* 2021). The efficiency of DBS depends on targeted neuroanatomical locations most important of which are: subcallosal cingulate gyrus (SCG), nucleus accumbens (NAc), ventral capsule/ventral striatum or anterior limb of internal capsule (ALIC), medial forebrain bundle (MFB), lateral habenula (LHb) and inferior thalamic peduncle (Cattarinussi *et al.* 2022). Newest studies show that modifying white matter tracts may be more efficient for antidepressant response to DBS than targeting gray matter areas (Dandekar *et al.* 2018).

Drug-resistant patients treated with DBS have reported sudden serenity whereas the research showed decreased blood flow in the Brodmann area 25 which activity is directly connected to the duration of depressive episodes. (Krauss *et al.* 2021; Figee *et al.* 2022). The abnormal metabolic activity of the subcallosal cingulate gyrus (SCG), including Brodmann area 25, is an important part of mechanisms of treatment-resistant depression and therefore SCG remains the most targeted region in DBS for treatment-resistant depression (Mayberg *et al.* 2005). Another study showed that DBS of habenula reduces depressive episodes and exhibits efficacy in working with the brain's antireward system (Hamani *et al.* 2010). Recent studies name Brodmann area 10 and amygdala as another targets crucial for efficacy of treatment with DBS (Zhang *et al.* 2022).

DBS also attenuates neuroinflammation as well as inhibits pro-inflammatory factors that may cause mood improvement (Zhu *et al.* 2021).

Studies showed that approximately 60% of refractory patients treated with DBS across different targets responded well to the treatment. However, the results vary significantly between different patients. (Guo *et al.* 2023). Study investigating the influence of DBS of

the nucleus accumbens on drug-resistant depressive patients. showed that almost 50% of examined patients responded well to the treatment and had their mental health stabilized for the time of four years (Krauss *et al.* 2021). The constant improvement of mental state throughout the years shows the effectiveness of DBS (Figee *et al.* 2022).

Despite the proven effectiveness (Figee *et al.* 2021) of DBS including improvement of mood, activity and ability to feel pleasure, there is a risk of inducing some negative psychotic symptoms. Even though the number of positive responding patients prevails, there are some described cases of maniac or even, conversely to its objective, depressive episode after using DBS. Depressive symptoms include suicidal thoughts or attempts and hence need to long-term monitor the patients subjected to DBS. Furthermore there is risk of neurosurgical complications such as infections or intracerebral hemorrhage (Krauss *et al.* 2021). The potential risks of using DBS need to be factored during selecting the treatment method for depressive patients.

Further studies need to be conducted in order to completely understand mechanisms of deep brain stimulation and its potential long-term health consequences as well as its safety and overall efficacy.

2. Potential Non-pharmacological Treatment Methods

Acupuncture

Acupuncture is a method of transcutaneous nerve stimulation used to treat many conditions. It is one of many prospective therapies for reducing the symptoms of depression. It is considered a type of effective and safe medical practice. Advantages of this method include low cost and negligible side effects. Acupuncture in combination with drug treatment has been proven to produce better therapeutic effects (Bergfeld *et al.* 2022) than the drug alone. It minimizes the side effects of antidepressants which include nausea, insomnia, weight gain and sexual dysfunction (Bergfeld *et al.* 2022). Although the mechanism and efficacy (Bergfeld *et al.* 2022) of acupuncture are not known with certainty, it is claimed to modulate neuroplasticity, improve synapse function and affect microglia (Yang *et al.* 2022). Acupuncture is among the non-pharmacological treatments for depression. There is a distinction between isolated therapy and complementary therapy, which can be done in two styles: manual acupuncture and electroacupuncture (Bergfeld *et al.* 2022; Wang *et al.* 2022). More commonly used in medical practice is the manual method, which involves the percutaneous insertion of a thin metal needle into an acupoint (Yang *et al.* 2022) followed by manipulation, needle heating and massage. Electroacupuncture (Wang *et al.* 2022) is based on electrical stimulation instead of manual manipulation and thus can generate more consistent and reproducible results (Bergfeld *et al.* 2022). Depression, as the world's most severe mental disorder (Bergfeld *et al.* 2022), is one of the heterogeneous disorders that have arisen due to multiple pathomechanisms. Abnormalities lie in inflammation and neuroplasticity, among others (Bergfeld *et al.* 2022). The cause of depression is unknown, but the brain is important in its pathogenesis. It is claimed that changes in brain structure, chemical imbalances (Ulloa 2021; Bergfeld *et al.* 2022) and physiological abnormalities are directly responsible for the symptoms of depression. Structural and functional abnormalities have been demonstrated in specific brain regions and connections that affect cognitive and emotional phenomena (Bergfeld *et al.* 2022) occurring in the hippocampus, medial prefrontal cortex, anterior cingulate cortex, amygdala and semilocular nucleus. This is initiated at the level of cellular aberrations, resulting in the reduction of the above-mentioned brain areas. Acupuncture can work by regulating biochemical pathways and also restoring neuronal structures in patients suffering from depression. The monoamine neurotransmitter serotonin [5-HT] is also suspected to be involved in pathomechanism. Serotonin is formed by the metabolism of the exogenous amino acid tryptophan. Exogenous, which

is supplied to the body with the diet. In the pathomechanism of depression, serotonin undergoes excessive feedback resorption at the nerve synapse (Ulloa 2021; Bergfeld *et al.* 2022). In addition, there is increased autoreceptor activity, which inhibits the release of serotonin into the synapse (Ulloa 2021). Using acupuncture, the postsynaptic receptor for serotonin can be upregulated, restoring synaptic plasticity while reducing symptoms of depression. It has been observed that antidepressant drug therapy significantly reduces serotonin levels. This is one of the ways in which acupuncture supports antidepressant drugs, by increasing levels of 'FUNCTIONAL SEROTONIN' (Moncrieff *et al.* 2023). However, the theory of serotonin's involvement in the pathomechanism of depression is disputed. Most studies do not conclude that reduced or absent serotonin activity is observed in depressed individuals (Ulloa 2021) relative to healthy individuals. Nonetheless, many researchers support the supposition that serotonin deficiency results in depressive symptoms for a number of reasons. In the central nervous system, the most important component of the immune system is microglia, which is activated by pathogens and also by damaged synapses and neurons. Microglia has two types proinflammatory M1 and anti-inflammatory M2 (Wang *et al.* 2022). It has been shown that microglia, in addition to protecting brain tissue, activated proinflammatory types as an important part of the pathophysiology of depression. The interaction between inflammation and the brain's immune system can induce an imbalance of serotonergic and noradrenergic neurotransmission. The action of microglia is largely based on the secretion of pro-inflammatory (Yang *et al.* 2022) cytokines. The neurodegeneration and DEPRESSIONAL DISORDERS induced by these molecules act in two ways. The first is by reducing the activity of the enzyme indoleamine 2,3-dioxygenase. As a result, what decreases is the level of serotonin. The second involves an imbalance of serotonergic and noradrenergic neurotransmission through the hypothalamic-pituitary-adrenal axis. The use of acupuncture has contributed to a reduction in plasma levels of pro-inflammatory cytokines and thus a reduction in symptoms of depression. For mild and moderate forms of depression, isolated acupuncture therapy is used. Data collected over the years show that acupuncture has such good effects that additional therapeutic methods (Bergfeld *et al.* 2022; Yang *et al.* 2022) are not necessary. This was proven during a multicenter, randomized, controlled clinical trial. The subjects included peri-menopausal women with associated, moderate depressive symptoms. One part received drug treatment, the other part acupuncture. There were no differences among the subjects. In both pharmacologically and non-pharmacologically treated patients, improvements in quality of life and relief of depressive symptoms were observed (Bergfeld *et al.* 2022). Because of this, acupuncture is a potentially effective treatment for mild and moderate depression. Severe forms of depression (Bergfeld *et al.* 2022) require pharmacological treatment. More than half of patients respond well to treatment while a significant proportion do not. In addition, 63% of those taking medication have experienced side effects (Bergfeld *et al.* 2022). More than half of patients respond well to treatment while a significant proportion do not. In addition, 63% of those taking medication experienced side effects (Bergfeld *et al.* 2022). A large proportion of patients were forced to discontinue treatment by adverse effects resulting in relapse. Combining drug treatment with acupuncture has been shown to have a positive effect. It may reduce side effects, although due to the small number of studies it remains questionable. A meta-analysis and systematic review involving 1.046 people in a randomized controlled clinical trial confirmed that acupuncture combined with a selective serotonin reuptake inhibitor has an early onset of action, is better tolerated and initiates a strong antidepressant effect.

Physical activity

Physical activity is believed to reduce the symptoms of depression and also show (Davidson *et al.* 2022, Correia *et al.* 2022) a preventive effect in the development of depressive disorders. Physical activity refers to any type of body movement induced by muscular work and resulting in energy expenditure (Correia *et al.* 2022). Although the relationship between activity and depression is not fully elucidated, exercise affects a number of biological and psychosocial processes that are related to (Saran *et al.* 2021) the pathophysiology of depression. The benefits of physical activity for depression outweigh the risk reduction (Saran *et al.* 2021). In addition, exercise affects the endocrine system, self-esteem, social support, and neuroplasticity in oxidative stress or inflammation. Most importantly, it induces a wide range of biological changes in the brain, in addition to its impact on psychiatric disorders, physical activity also affects comorbidities that have contributed to or exacerbate the development of depression. An example is that exercise can reduce the risk of cardiovascular disease, (Saran *et al.* 2021; Correia *et al.* 2022) which is elevated in people with depression. It has been discovered that a cycle of biochemical transformations occurring under the influence of skeletal muscle activity prevents the adverse effects of stress by increasing production from brain nerve growth factor. This factor stimulates cell differentiation, promotes neuronal function by stimulating repair processes and also enhances memory pathways, thus having a beneficial effect on affective and cognitive functioning and the patient's daily activities. An example is people who do not engage in physical activity, where mental disorders are more likely to occur. It is possible to quantify the population burden of depression (Davidson *et al.* 2022) that is associated with too little physical activity and the potential impact of activity interventions on public health. Therefore, Mendelian randomization studies using the whole genome were conducted to support potential causal inference. Mendelian randomization is a surrogate method of potential causal inference that addresses genetic variation as a natural experiment in which individuals are generally assigned to higher and lower average levels of non-genetic exposure over their lifetime. Higher levels of physical activity were associated with a reduced likelihood of major depression. Genome-wide association study summary data were available for a combined sample of 611.583 adult participants. Mendelian randomization evidence suggests a preventive association between accelerometer-based activity and major depressive disorder (Kandola *et al.* 2019). Using genetic instruments identified from large-scale whole-genome association, solid evidence supports a protective relationship between physical activity (Kandola *et al.* 2019). and the risk of depressive disorder manifestation. Although sports have a positive effect on depression, (Davidson *et al.* 2022) some studies reveal that depression can cause a decrease in physical activity. This is mainly true for the severe form of the disease, where movement causes great suffering. Patients may not be able to cope with (Choi *et al.* 2019) the simplest activities. It has also been suggested that physical activity may in some way contribute to the development (Kandola *et al.* 2019; Davidson *et al.* 2022) of depression. Exercise that is characterized by excessive frequency and intensity, that is, exercise that exceeds the needs and capabilities of the body, may be associated with an increase (Choi *et al.* 2019) in oxidative stress. This stress is of great importance in the pathomechanism of depression. The type of activity is also important. Of the various physical activities, aerobic exercise is the most effective, and the most widely used. The effect of aerobic activities on modifying the volume of the hippocampus, which is reduced (Correia *et al.* 2022) in depressed patients, has been confirmed. In addition, environmental conditions are of paramount importance, as noise or neighborhood deprivation can reduce the mental health benefits of

activity. A recent meta-analysis of 49 prospective cohort studies comprising 1.837.794 averaged by the number of people exposed during the follow-up period and the duration of follow-up found that people with high physical activity were 17% less likely to be depressed than those with low physical activity (Zhang *et al.* 2019). Meta-analyses conducted collectively on a sample of 1.282 seniors with symptoms of depressive disorders show that the exercise used reduced the severity of the disorder and also improved the subjects' physical fitness. Although few empirical studies show evidence of ineffectiveness or confirm the low importance of physical activity in reducing symptoms of depression. This research focused on analyzing the correlation between physical activity and mental health attests that higher physical activity is associated with a lower risk of depression-specific symptoms, especially in adolescents (Wienicke *et al.* 2023). 1 in 9 cases of depression could be avoided if everyone in the population was physically active (Saran *et al.* 2021) at the level of current recommendations. Therefore, therapists and physicians should encourage their clients to exercise of all kinds to fill in the gaps in engaging in poor activities that lead to depression.

Probiotics

Recent studies have investigated the influence of intestinal microflora on mental state. Clinical studies on animals showed that probiotics containing particular bacteria strain influence brain operation and the results of behavioral tests proving thereby the connection between microbial gut bacteria and the central nervous system. This two-way communication called 'gut-brain axis' explains why supplementation of probiotics may be considered as a potential alternative therapy in treatment of depression (Sudak 2012).

The microbiota varies depending on the patient's health state. For instance, children diagnosed with autism had an increased number of Clostridium bacteria in comparison with healthy children (Herman 2019).

Irritable bowel syndrome suggests a connection between mental illnesses and inadequate bowel function since patients with IBS have increased depression morbidity rate (Finegold *et al.* 2022).

There are many examples in literature showing (Fond *et al.* 2014) differences in gut flora of depressive patients compared to the healthy controls. Tests on animals showed that intestinal bacterial colonization is crucial for proper development of both enteric and the central nervous system (Alli *et al.* 2022). The microbiota and probiotics both increase the intestinal wall's integrity and thus have a positive anti-inflammatory effect. There is a significant connection between inflammation and depression hence probiotics are a promising treatment method for treatment-resistant depression. Another way of influencing mental health by probiotics, except for regulation of inflammatory markers, is regulation of serotonin pathways (Minayo *et al.* 2021). Clinical trials during studies consisted of administering the following commensal bacterial stains: Lactobacilli (L.), Bifidobacteria (B.), Streptococcus (S.), or Lactococcus. Half of studies evaluating effects of daily probiotic intake on depression (Alli *et al.* 2022) reported improvement in terms of depressive episodes whereas the other half reported no change regarding depressive symptoms. However, some of the bacteria such as L. Plantarum P8 or L. Plantarum DR7 from the studies that concluded no change had positive effect on other symptoms for example reduced stress and anxiety, reduced cortisol level or reduced proinflammatory cytokines level. Depressed patients who were administered probiotics containing L. casei, L. acidophilus, and B. bifidum experienced general mood improvement (Alli *et al.* 2022). Another study investigating the influence of consuming yogurt containing different types of Lactobacilli and Bifidobacteria by healthy petrochemical workers revealed significant mental health improvement.

Probiotic administration was however not always successful and many studies showed

no difference in general mood of patients treated with probiotics (Sudak 2012; Alli *et al.* 2022).

Further studies need to be conducted in order to completely explore the details of gut-brain axis and possible long-term influence of using probiotic strains on mental health. The major differences in outcomes of various studies as well as too small groups of treated patients and other limitations such as patients' diet or assessment of the dose (Sudak 2012) preclude drawing a definitive conclusion regarding the effectiveness of probiotics in treatment of depression. However, (Minayo *et al.* 2021) probiotics, especially those containing Lactobacillus seem to have an effect on depression.

Yoga and mindfulness

Recently yoga and mindfulness have gained importance in terms of non-pharmacological depression treatment.

Mindfulness-based interventions that is MBIs (Liu *et al.* 2019) is an alternative therapy which is administered in order to improve the quality of life of patients with depression especially in terms of social and cognitive aspects. Mindfulness-based stress reduction (MBSR) program is based on focusing on the present bodily situation and noticing both internal and external experiences and connection between them, for example correlation between mental state and perceived physical pain (Chayadi *et al.* 2022). This intentional awareness has thereby a positive influence on both physical and mental conditions. Slightly changed version of MBSR which is MBCT (mindfulness-based cognitive therapy) was incorporated into treatment of depression and showed a high success rate (Chayadi *et al.* 2022). MBIs show how to accept emotional struggles and manage current mental state based on the interrelationship between the body and the mind (Chayadi *et al.* 2022). In a study conducted on oncology patients MBIs reduced symptoms of depression and anxiety. However, due to the individual patients' differences, low amount of studies and no proven long term effectiveness the results need to be further proven (Liu *et al.* 2019). Studies show that MBIs used with children and adolescents (Wilkos *et al.* 2013) as well as university students (Dunning *et al.* 2019) can also improve their mental health and reduce symptoms of depression.

Yoga is also a method used for mental health protection including treatment of depression. Historical articles prove the effectiveness of yoga exercises on psychiatric disorders (Gallo *et al.* 2023). Yoga helps to activate the parasympathetic nervous system and thereby induces relaxation (Gallo *et al.* 2023) and calmness (Żok *et al.* 2022). Yoga is also due to its low exercise intensity a suitable activity for pregnant women with depression who are often excluded from other treatment methods including antidepressants. Practicing prenatal yoga had an alleviating influence on mental health of pregnant women with depression, however had no effect on depression scores for those without depression (Gong *et al.* 2015). Another study showed the efficiency of mind-body exercise such as yoga on Chronic Obstructive Pulmonary Disease patients in terms of depression (Lin *et al.* 2022).

These techniques show how to accept emotional struggles and manage current mental state (Chayadi *et al.* 2022) based on the interrelationship between the body and the mind. These alternative methods seem to be efficient in terms of treating depression, however further studies need to be conducted in order to completely confirm their effectiveness. Since no negative effects were noticed, yoga (Żok *et al.* 2022) and mindfulness can be used as a supporting therapy.

Psychodelics

Due to a review, 'Prevalence and clinical course of depression' by Derek Richards (Li *et al.* 2019) one in three of people who are suffering from a major depressive disorder (MDD) will experience more than one depressive episode in their lifetime. Also a half of patients with depressive disorder do not respect policy of

antidepressants intake as soon as 6 months after initiation of treatment (Richards 2011). Relatedly, new treatments for depression are needed. Especially for those who do not respond to available antidepressants.

Psychedelic substances are a group of psychoactive substances that are associated with altered state of consciousness and perception (Solmi *et al.* 2022). There are two main categories of psychedelics; classic serotoninergic and atypical. Classic serotonergic psychodelics act on 5-HT2A receptors and we can distinguish psilocybin, N,N-dimethyltryptamine (DMT), ayahuasca, lysergic acid diethylamide (LSD). 3.4-methylenedioxymethamphetamine (MDMA) is an atypical psychodelic, that act on various receptors.

It is observed that more people are interested in psychedelics as therapy for depression in recent years. Lysergic acid diethylamide (LSD) and psilocybin were one of firsts which were used for treating drug resistant depression. This modulating property on the serotonergic neurotransmission system allows use psychodelics also in the treatment of major depressive disorder (MDD).

Psilocybin exerts its effects through agonism of the serotonin 5-HT2A receptors (González-Maeso *et al.* 2007; Halberstadt and Geyer 2011; Nichols 2016). The 5-HT2A receptors are necessary for the psychedelic experience, as the subjective effects of psilocybin seem to be blocked by 5-HT2A antagonists (Madsen *et al.* 2019). Psilocybin also has affinity albeit to a smaller extent, for several other serotonin receptors such as 5-HT1A and 5-HT2C (Vollenweider *et al.* 1998; Erkizia-Santamaria *et al.* 2022).

The serotonergic system plays a crucial role in regulating complex emotional behaviors (Rickli *et al.* 2016). For example, post-mortem analyses of depressed and suicidal individuals show increased expression of cortical 5-HT2A receptors (Pandey *et al.* 2002; Cools *et al.* 2018), while long-term antidepressant use is associated with decreased 5-HT2A receptor density (Shelton *et al.* 2009). Serotonin is involved in the feedback inhibition of the amygdala through the medial prefrontal cortex. (Gòmez-Gil *et al.* 2004) Amygdala hyperactivity is associated with depressive symptoms, and its normalization has been observed with antidepressant treatment (Fisher *et al.* 2009). As serotonergic agonists, psychedelics enhance the inhibition of the amygdala, and the resulting decrease in amygdala reactivity is linked to improved mood (Carhart-Harris *et al.* 2012; Sladky *et al.* 2015; Kraehenmann *et al.* 2016).

Ayahuasca

Ayahuasca is a traditional Amazonian brew which is made from the Banisteriopsis caapi vine and the Psychotria viridis leaf. The psychoactive effects are connected with specific alkaloids. Banisteriopsis caapi contains β-carboline alkaloids such as harmine, tetrahydroharmine, and harmaline, which are inhibitors of monoamine oxidase-A (MAO-A). MAO-A is an enzyme that normally degrades DMT in the digestive system.

This inhibition allows DMT to be orally active. Thereby it exerts its psychoactive effects during digestion as part of ayahuasca. Psychotria viridis contains N,N-Dimethyltryptamine (DMT), which has a powerful psychoactive compound. DMT is known as a classic serotonergic psychedelic, primarily acting as an agonist at the 5-HT1A and 5-HT2A receptors.

Additionally, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) is another related short-acting serotonergic psychedelic. It is more like DMT, because of primarily acting as an agonist at the 5-HT1A and 5-HT2A receptors. In contrast, it has a lower binding affinity for dopamine receptors and norepinephrine transporters.

The interactions with the 5-HT receptors are central to the psychoactive and hallucinogenic effects of these compounds, contributing to the unconscious states during ayahuasca use (Carhart-Harris *et al.* 2012).

An open-label (Kalfas *et al.* 2023) revealed that Ayahuasca impacts on a reduction up

to 82% in depressive scores between baseline and 1, 7 and 21 days after drug intake. It was according to the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Anxious-Depression subscale of the Brief Psychiatric Rating Scale (BPRS).

The most significant impact was observed on depressed mood, feelings of guilt and suicidal ideation, which are typical depressive symptoms. (Osório *et al.* 2015).

Compared to placebo, ayahuasca also increased BDNF levels in people with treatment resistant depression and healthy controls (Harvey 2003). This investigation was correlated with reduction in MADRS scores ($rho = -0.55$, $p < .05$). It has also been suggested that serotonergic psychedelics may possess a unique ability to promote plasticity compared to other serotonergic agents. (Carhart-Harris *et al.* 2012; Muttoni *et al.* 2019).

Psilocybin

Psilocybin is a naturally occurring plant alkaloid which can be found in mushroom species, also known as 'magic mushroom,' It is also considered a prodrug of psilocin. Psilocybin influences on agonism of the serotonin 5-HT2A receptors. (González-Maeso *et al.* 2007; Halberstadt and Geyer 2011; Nichols 2016). The 5-HT2A receptors are necessary for the psychedelic experience, because that subjective effects of psilocybin are seem to be blocked by 5-HT2A antagonists (Carhart-Harris *et al.* 2012; Madsen *et al.* 2019).

Psilocybin influences on cognitive flexibility, cortical neural plasticity, and antidepressant responses in animals (Vaidya *et al.* 1997; Harvey 2003; Buchborn *et al* 2014; Vargas *et al* 2023).

The results of 'The experimental effects of psilocybin on symptoms of anxiety and depression': found that half of psilocybin antidepressant effect occurs at doses of 10.13 mg/70 kg, and 95% of the antidepressant effect occurs at doses of 41.14 mg/70 kg, achieving the optimal therapeutic effect. However, these results must be interpreted with caution, as with the exclusion of the only study including treatment-resistant patients (Hanks and Gonzales-Maeso 2013). Research showed that resistant patients mostly respond to higher doses of psilocybin (40 mg/kg).

Among the pool of patients with secondary depression, only 16% of patients presented MDD as a 'primary' diagnosis, other patients presenting adjustment and anxiety disorders.

These effects have also been observed in healthy volunteers, with psilocybin causing sustained improvements in wellbeing and optimism (Goodwin *et al.* 2022). This compound has a well established physiological and psychological safety profile, and has been rated one of the least harmful and possibly 'most beneficial' drugs of potential misuse by experts (Carhart-Harris and Nutt 2013; Griffiths *et al.* 2018).

Additionally animal studies have proved that psilocybin has a low addiction and physical dependence potential (Hasler *et al.* 2004). National surveys report showed low rates of abuse (European Monitoring Center for Drugs and Drug Addiction). In RCTs conditions, psilocybin appears to be well tolerated in the long term (Studerus *et al.* 2011; Griffiths *et al.* 2016; Johnson *et al.* 2018).

For patients who present a process of anxiety or psychotic symptoms, we can assume that higher doses of psilocybin may reduce therapeutic effectiveness by inducing dysphoric mood states, such as anxiety and fearful delusions. It can be primarily due to phenomena like ego-disintegration and loss of self-control (Griffiths *et al.* 2016; Perez *et al.* 2023). It is essential to note the paradoxical effect of serotonergic psychedelics, which can increase feelings of anxiety (Stoliker *et al.* 2022). The nature of psychedelic experiences is dependent on doses. Higher doses are associated with ego dissolution and potentially leading to a sense of loss of control, subsequent anxiety, or short-term psychosis-like symptoms (Carhart-Harris *et al.* 2014).

Neurobiologically, stimulation of 5-HT2A receptors has been linked to positive and negative aspects of the acute psychedelic state

including positive mood, anxiety, and psychotic symptoms. Carhart-Harris and colleagues propose the 'entropic brain' hypothesis by suggesting that increased cognitive entropy may explain paradoxical psychological effects (Griffiths *et al.* 2008; Hirschfeld and Schmidt 2021). These potential reactions prove that patients will achieve the ED95 for depressive symptom reduction at lower doses of psilocybin.

Additionally, Li and colleagues, in their meta-analysis, reported that the first or unique dose of psilocybin received was generally more impactful in decreasing depressive symptoms compared to subsequent doses (Rankaduwa and Owen 2023). Patients naive to hallucinogens might show a more significant response to psilocybin due to the novelty of the experience (Li *et al.* 2022). However, most studies provide narrow information on participants who use hallucinogens all their lifetime .

Therefore, the optimal dose of psilocybin for treating depression varies significantly among different patient subgroups. Caution should be exercised regarding dosage, especially for patients with psychiatric disorders other than depression (Studerus *et al.* 2011).

LSD

In contrast, lysergic acid diethylamide (LSD) is a semisynthetic psychedelic compound (Li *et al.* 2022). Reports from mid-twentieth century indicate that cancer patients who received LSD experienced profound psychospiritual insights. They led to long-standing improvements in mood and anxiety (Passie *et al.* 2008; Haijen *et al.* 2018). LSD is considered to be emotionally more intense than psilocybin. Also it has a higher cause of paranoia. Although high doses can result in severe anxiety or panic attacks. These adverse effects are generally prevented in a clinical setting with proper psychological support (Kast 1967).

LSD is primarily a 5-HT2A receptor partial agonist and a 5-HT1A receptor agonist but has also been shown to bind to 5-HT2C receptors (Egan *et al.* 1998; Osório *et al.* 2015; Das *et al.* 2016, De Gregorio *et al.* 2018).

LSD positively altered the processing of emotional information by decreasing the recognition of fearful and sad faces and enhancing emotional empathy and prosociality. We are aware of no other published data on the acute effects of LSD on emotion processing.

LSD (lysergic acid diethylamide) has been found to impair the recognition of negative emotions while enhancing emotional empathy, particularly in response to positive emotional situations.

Furthermore, LSD demonstrates prosocial effects, both subjectively and in behavioral assessments. These findings in healthy individuals suggest that LSD-assisted psychotherapy may be beneficial for patients, as it is expected to reduce the perception of negative emotions and strengthen the therapeutic alliance (Passie *et al.* 2008).

Summary of psychedelics

As we can observe, psychedelic administration causes statistically significant impact in reduction of depression and anxiety symptoms. These findings are consistent with prior investigations conducted on animals, healthy subjects, and anecdotal testimonials. (Kast *et al.* 1967; Richards *et al.* 1977; Riba *et al.* 2001; Hilber and Chapillon 2005; Farzin and Mansouri 2006; Santos *et al.* 2007; Griffiths *et al.* 2008; Fortunato *et al.* 2010). Visible improvement suggests a genuine therapeutic efficacy. What is more, the lack of significant reduction of depressing symptoms in control patients indicates that the antidepressant and anxiolytic effects can be attributed to psychedelic intervention. Participants also described the experience as spiritually meaningful, resulting in decreased feeling of hopelessness as well as improved a quality of life. Psychedelics' ability to provide acute symptom relief in one day is advantageous, especially when we compare it to current antidepressants, which take several weeks to work. This is because antidepressants delayed therapeutic effects can lead to non-compliance and contribute to increased morbidity

(Tylee *et al.* 2007; Machado-Vieira *et al.* 2010). Moreover, psychedelics' beneficial effects are maintained with impressive response rates for several months. This could mean that by comparison to the typical pharmacotherapy, administration is less frequent. In conjunction to the fact that exposure to treatment is monitored, it could help to overcome treatment resistance stemming from non-compliance (Kalfas *et al.* 2023).

Conclusions

While the current focus is on alternative non-pharmacological methods for treating depression, it is worth remembering the already established options. ECT, psychotherapy, VNS, TMS, and DBS have been implemented and recognized for decades. They are not only effective but also widespread. However, the rising percentage of depression cases has created a demand for new treatment methods. Alternative approaches for treating depressive disorders emerge annually. Possibilities range from solutions found in traditional Chinese medicine to unexpected branches of pharmacology, as shown in the 'psychedelics' section. The impact of lifestyle and mindfulness on cognitive processes and well-being is also significant. Some of the methods presented are widely accessible and affordable, making them available to patients and specialists. Non-pharmacological treatment methods have been shown to cause significantly fewer side effects compared to traditional approaches, such as antidepressant drugs. Moreover, they can be equally effective. However, more clinical trials are needed to prove the efficacy and safety of non-pharmacological methods for treating depression. Hopefully, with access to more advanced technology and an increasingly open-minded approach to the holistic nature of the human mind, scientists will discover groundbreaking solutions.

REFERENCES

Żok, A., Zapała, J., Baum, E. (2021), *'Activities based on yoga techniques in psychiatric treatment in Poland in a historical context.'* Psychiatria Polska, 56(6), pp. 1405–1416.

Alli, S.R., Gorbovskaya, I., Liu, J.C.W., Kolla, N.J., Brown, L., Müller, D.J. (2022), *'The Gut Microbiome in Depression and Potential Benefit of Prebiotics, Probiotics and Synbiotics: A Systematic Review of Clinical Trials and Observational Studies.'* International Journal of Molecular Sciences, [online] 23(9), p. 4494.

Antosik-Wójcińska, A., Święcicki, Ł. (2015), *'The use of DBS stimulation in mental disorders – opportunities and risks.'* Psychiatria Polska, 49, 791–800.

Badran, B.W., Mithoefer, O.J., Summer, C.E., LaBate, N.T., Glusman, C.E., Badran, A.W., DeVries, W.H., Summers, P.M., Austelle, C.W., McTeague, L.M., Borckardt, J.J., George, M.S. (2018), *'Short trains of transcutaneous auricular vagus nerve stimulation (taVNS) have parameter-specific effects on heart rate.'* Brain Stimulation, 11(4), pp. 699–708.

Barker, A.T., Jalinous, R., Freeston, I.L. (1985), *'Non-invasive magnetic stimulation of human motor cortex.'* The Lancet, 325(8437), pp. 1106–1107.

Bergfeld, I.O., Ooms, P., Lok, A., de Rue, L., Vissers, P., de Knijff, D., Horst, F., Beute, G., van den Munckhof, P., Schuurman, P.R. Denys, D. (2022), *'Efficacy and quality of life after 6–9 years of deep brain stimulation for depression.'* Brain Stimulation, [online] 15(4), pp. 957–964.

Buchborn, T., Schröder, H., Höllt, V., Grecksch, G. (2014), *'Repeated lysergic acid diethylamide in an animal model of depression: Normalisation of learning behaviour and hippocampal serotonin 5-HT2signalling.'* Journal of Psychopharmacology, 28(6), pp. 545–552.

Bulteau, S., Laurin, A., Pere, M., Fayet, G., Thomas-Ollivier, V., Deschamps, T., Auffray-Calvier, E., Bukowski, N., Vanelle, J.-M., Sébille, V., Sauvaget, A. (2022), *'Intermittent theta burst stimulation (iTBS) versus 10 Hz high-frequency repetitive transcranial magnetic stimulation (rTMS) to alleviate treatment-resistant unipolar depression: A randomized controlled trial (THETA-DEP).'* Brain Stimulation, 15(3), pp. 870–880.

Butt, M.F., Albusoda, A., Farmer, A.D., Aziz, Q. (2020), *'The anatomical basis for transcutaneous auricular vagus nerve stimulation.'* Journal of Anatomy, 236(4), pp. 588–611.
Carhart-Harris, R.L., Nutt, D.J. (2013), *'Experienced Drug Users Assess the Relative Harms and Benefits of Drugs: A Web-Based Survey.'* Journal of Psychoactive Drugs, 45(4), pp. 322–328.
Carhart-Harris, R.L., Erritzoe, D., Williams, T., Stone, J.M., Reed, L.J., Colasanti, A., Tyacke, R.J., Leech, R., Malizia, A.L., Murphy, K., Hobden, P., Evans, J., Feilding, A., Wise, R.G., Nutt, D.J. (2012), *'Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin.'* Proceedings of the National Academy of Sciences, 109(6), pp. 2138–2143.
Carhart-Harris, R.L., Leech, R., Hellyer, P.J., Shanahan, M., Feilding, A., Tagliazucchi, E., Chialvo, D.R., Nutt, D. (2014), *'The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs.'* Frontiers in Human Neuroscience, 8(20).
Carreno, F.R., Frazer, A. (2017), *'Vagal Nerve Stimulation for Treatment-Resistant Depression.'* Neurotherapeutics, 14(3), pp. 716–727.
Cattarinussi, G., Moghaddam, H.S., Aarabi, M.H., Squarcina, L., Sambataro, F., Brambilla, P., Delvecchio, G. (2022), *'White Matter Microstructure Associated with the Antidepressant Effects of Deep Brain Stimulation in Treatment-Resistant Depression: A Review of Diffusion Tensor Imaging Studies.'* International Journal of Molecular Sciences, 23(23), p. 15379.
Chayadi, E., Baes, N., Kiropoulos, L. (2022), *'The effects of mindfulness-based interventions on symptoms of depression, anxiety, and cancer-related fatigue in oncology patients: A systematic review and meta-analysis.'* PLoS One, 17(7), p. e0269519.
Chen, Y., Guillemin, G.J. (2009), *'Kynurenine Pathway Metabolites in Humans: Disease and Healthy States.'* International Journal of Tryptophan Research, [online] 2, p.IJTR.S2097.
Choi, K.W., Chen, C.-Y., Stein, M.B., Klimentidis, Y.C., Wang, M.-J., Koenen, K.C., Smoller, J.W. (2019), *'Assessment of Bidirectional Relationships Between Physical Activity and Depression Among Adults.'* JAMA Psychiatry, [online] 76(4), p. 399.
Conway, C.R., Sheline, Y.I., Chibnall, J.T., George, M.S., Fletcher, J.W., Mintun, M.A. (2006), *'Cerebral blood flow changes during vagus nerve stimulation for depression.'* Psychiatry Research: Neuroimaging, 146(2), pp. 179–184.
Cools, R., Roberts, A.C., Robbins, T.W. (2008), *'Serotoninergic regulation of emotional and behavioural control processes.'* Trends in Cognitive Sciences, 12(1), pp. 31–40.
Correia, A.S., Vale, N. (2022), *'Tryptophan Metabolism in Depression: A Narrative Review with a Focus on Serotonin and Kynurenine Pathways.'* International Journal of Molecular Sciences, 23(15), p. 8493.
Cristancho, P., Kamel, L., Araque, M., Berger, J., Blumberger, D.M., Miller, J.P., Barch, D.M. Lenze, E.J. (2020), *'iTBS to Relieve Depression and Executive Dysfunction in Older Adults: An Open Label Study.'* The American Journal of Geriatric Psychiatry [online].
Dandekar, M.P., Fenoy, A.J., Carvalho, A.F., Soares, J.C., Quevedo, J. (2018), *'Deep brain stimulation for treatment-resistant depression: an integrative review of preclinical and clinical findings and translational implications.'* Molecular Psychiatry, [online] 23(5), pp. 1094–1112.
Das, S., Barnwal, P., Ramasamy, A., Sen, S.,-Mondal, S. (2016), *'Lysergic acid diethylamide: a drug of 'use'?'* Therapeutic Advances in Psychopharmacology, [online] 6(3), pp. 214–228.
Davidson, M., Rashidi, N., Nurgali, K., Apostolopoulos, V. (2022), *'The Role of Tryptophan Metabolites in Neuropsychiatric Disorders.'* International Journal of Molecular Sciences, 23(17), p. 9968.
De Gregorio, D., Enns, J.P., Nuñez, N.A., Posa, L. and Gobbi, G. (2018), *'d-Lysergic acid diethylamide, psilocybin, and other classic hallucinogens: Mechanism of action and potential therapeutic applications in mood disorders.'* Progress in Brain Research, 242, pp. 69–96.
De Risio, L., Borgi, M., Pettorruso, M., Miuli, A., Ottomana, A.M., Sociali, A., Martinotti, G., Nicolò, G., Macrì, S., di Giannantonio, M.

Zoratto, F. (2020), *'Recovering from depression with repetitive transcranial magnetic stimulation (rTMS): a systematic review and meta-analysis of preclinical studies.'* Translational Psychiatry, [online] 10(1), pp. 1–19.
Dietrich, S., Smith, J., Scherzinger, C., Hofmann-Preiß, K., Freitag, T., Eisenkolb, A., Ringler, R. (2008), *'A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI / Funktionelle Magnetresonanztomographie zeigt Aktivierungen des Hirnstamms und weiterer zerebraler Strukturen unter transkutaner Vagusnervstimulation.'* Biomedizinische Technik/Biomedical Engineering, 53(3), pp. 104–111.
Dunning, D.L., Griffiths, K., Kuyken, W., Crane, C., Foulkes, L., Parker, J., Dalgleish, T. (2019), *'Research Review: The effects of mindfulness-based interventions on cognition and mental health in children and adolescents – a meta-analysis of randomized controlled trials.'* Journal of Child Psychology and Psychiatry, [online] 60(3), pp. 244–258.
Egan, C.T., Herrick-Davis, K., Miller, K., Glennon, R.A., Teitler, M. (1998), *'Agonist activity of LSD and lisuride at cloned 5HT 2A and 5HT 2C receptors.'* Psychopharmacology, 136(4), pp. 409–414.
Ekman, C.J., Popiolek, K., Bodén, R., Nordenskjöld, A., Lundberg, J. (2023), *'Outcome of transcranial magnetic intermittent theta-burst stimulation in the treatment of depression – A Swedish register-based study.'* Journal of Affective Disorders, [online] 329, pp. 50–54.
Elger, G., Hoppe, C., Falkai, P., Rush, A.John., Elger, C.E. (2000), *'Vagus nerve stimulation is associated with mood improvements in epilepsy patients.'* Epilepsy Research, 42(2-3), pp. 203–210.
Erkizia-Santamaría, I., Alles-Pascual, R., Horrillo, I., Meana, J.J., Ortega, J.E. (2022), *'Serotonin 5-HT2A, 5-HT2c and 5-HT1A receptor involvement in the acute effects of psilocybin in mice. In vitro pharmacological profile and modulation of thermoregulation and head-twich response.'* Biomedicine & Pharmacotherapy, [online] 154, p. 113612.
Farzin, D., Mansouri, N. (2006), *'Antidepressant-like effect of harmane and other ß-carbolines in the mouse forced swim test.'* European Neuropsychopharmacology, 16(5), pp. 324–328.
Figee, M., Riva-Posse, P., Choi, K.S., Bederson, L., Mayberg, H.S., Kopell, B.H. (2022), *'Deep Brain Stimulation for Depression.'* Neurotherapeutics, 19(4), pp. 1229–1245.
Figee, M., Riva-Posse, P., Choi, K.S., Bederson, L., Mayberg, H.S., Kopell, B.H. (2022), *'Deep Brain Stimulation for Depression.'* Neurotherapeutics, 19(4), pp. 1229–1245.
Finegold, Sydney M., Molitoris, D., Song, Y., Liu, C., Vaisanen, M., Bolte, E., McTeague, M., Sandler, R., Wexler, H., Marlowe, Elizabeth M., Collins, Matthew D., Lawson, Paul A., Summanen, P., Baysallar, M., Tomzynski, Thomas J., Read, E., Johnson, E., Rolfe, R., Nasir, P., Shah, H. (2002), *'Gastrointestinal Microflora Studies in LateOnset Autism.'* Clinical Infectious Diseases, 35(s1), pp. S6–S16.
Fisher, P.M., Meltzer, C.C., Price, J.C., Coleman, R.L., Ziolko, S.K., Becker, C., Moses-Kolko, E.L., Berga, S.L., Hariri, A.R. (2009), *'Medial Prefrontal Cortex 5-HT2A Density Is Correlated with Amygdala Reactivity, Response Habituation, and Functional Coupling.'* Cerebral Cortex, 19(11), pp. 2499–2507.
Fitzgerald, P.B. (2013), *'Non-pharmacological biological treatment approaches to difficult-to-treat depression.'* Medical Journal of Australia, 199(S6).
Fond, G., Loundou, A., Hamdani, N., Boukouaci, W., Dargel, A., Oliveira, J., Roger, M., Tamouza, R., Leboyer, M. and Boyer, L. (2014), *'Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis.'* European Archives of Psychiatry and Clinical Neuroscience, 264(8), pp. 651–660.
Fortunato, J.J., Réus, G.Z., Kirsch, T.R., Stringari, R.B., Fries, G.R., Kapczinski, F., Hallak, J.E., Zuardi, A.W., Crippa, J.A. Quevedo, J. (2010), *'Chronic administration of harmine elicits antidepressant-like effects and increases BDNF levels in rat hippocampus.'*

Journal of Neural Transmission, 117(10), pp. 1131–1137.

Frangos, E., Ellrich, J., Komisaruk, B.R. (2015), *'Non-invasive Access to the Vagus Nerve Central Projections via Electrical Stimulation of the External Ear: fMRI Evidence in Humans.'* Brain Stimulation, 8(3), pp. 624–636.

Gallo, G.G., Curado, D.F., Machado, M.P.A., Espíndola, M.I., Scattone, V.V., Noto, A.R. (2023), *'A randomized controlled trial of mindfulness: effects on university students' mental health.'* International Journal of Mental Health Systems, [online] 17(1), pp. 1–12.

Gautam, M., Tripathi, A., Deshmukh, D., Gaur, M. (2020), *'Cognitive behavioral therapy for depression.'* Indian Journal of Psychiatry, [online] 62(8), pp. 223–229.

George, M.S., Lisanby, S.H., Avery, D., McDonald, W.M., Durkalski, V., Pavlicova, M., Anderson, B., Nahas, Z., Bulow, P., Zarkowski, P., Holtzheimer, P.E., Schwartz, T. Sackeim, H.A. (2010), *'Daily Left Prefrontal Transcranial Magnetic Stimulation Therapy for Major Depressive Disorder.'* Archives of General Psychiatry, 67(5), p. 507.

George, M.S., Wassermann, E.M., Williams, W.A., Callahan, A., Ketter, T.A., Basser, P., Hallett, M., Post, R.M. (1995), *'Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression.'* NeuroReport, 6(14), pp. 1853–1856.

Gómez-Gil, E., Cristóbal Gastó, Carretero, M., Diaz-Ricart, M., Manel Salamero, Ricard Navinés, Gines Escolar (2004), *'Decrease of the platelet 5-HT2A receptor function by long-term imipramine treatment in endogenous depression.'* 19(4), pp. 251–258.

Gong, H., Ni, C., Shen, X., Wu, T., Jiang, C. (2015), *'Yoga for prenatal depression: a systematic review and meta-analysis.'* BMC Psychiatry, 15(1).

González-Maeso, Javier *et al.* (2007), *'Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior.'* Neuron vol. 53,3: 439–452.

Goodwin, G.M., Aaronson, S.T., Alvarez, O., Arden, P.C., Baker, A., Bennett, J.C., Bird, C., Blom, R.E., Brennan, C., Brusch, D., Burke, L., Campbell-Coker, K., Carhart-Harris, R., Cattell, J., Daniel, A., DeBattista, C., Dunlop, B.W., Eisen, K., Feifel, D., Forbes, M. (2022), *'Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression.'* New England Journal of Medicine, [online] 387(18), pp. 1637–1648.

Griffiths, R., Richards, W., Johnson, M., McCann, U., Jesse, R. (2008), *'Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later.'* Journal of Psychopharmacology, 22(6), pp. 621–632.

Griffiths, R., Richards, W., Johnson, M., McCann, U., Jesse, R. (2008), *'Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later.'* Journal of Psychopharmacology, 22(6), pp. 621–632.

Griffiths, R.R., Johnson, M.W., Carducci, M.A., Umbricht, A., Richards, W.A., Richards, B.D., Cosimano, M.P. and Klinedinst, M.A. (2016), *'Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial.'* Journal of Psychopharmacology, 30(12), pp. 1181–1197.

Guo, B., Zhang, M., Hao, W., Wang, Y., Zhang, T. and Liu, C. (2023), *'Neuroinflammation mechanisms of neuromodulation therapies for anxiety and depression.'* Translational Psychiatry, 13(1).

Haijen, E.C.H.M., Kaelen, M., Roseman, L., Timmermann, C., Kettner, H., Russ, S., Nutt, D., Daws, R.E., Hampshire, A.D.G., Lorenz, R. Carhart-Harris, R.L. (2018), *'Predicting Responses to Psychedelics: A Prospective Study.'* Frontiers in Pharmacology, 9(897).

Halberstadt, A.L., Geyer, M.A. (2011), *'Multiple receptors contribute to the behavioral effects of indoleamine hallucinogens.'* Neuropharmacology, 61(3), pp. 364–381.

Hamani, C., Mayberg, H., Stone, S., Laxton, A., Haber, S., Lozano, A.M. (2011), *'The Subcallosal Cingulate Gyrus in the Context of Major Depression.'* Biological Psychiatry, 69(4), pp. 301–308.

Hanks, J.B., González-Maeso, J. (2012), *'Animal Models of Serotonergic* Psychedelics. ACS Chemical Neuroscience.' 4(1), pp. 33–42.
Harvey, J.A. (2003), *'Role of the Serotonin 5-HT2A Receptor in Learning.'* Learning & Memory, 10(5), pp. 355–362.
Hasler, F., Grimberg, U., Benz, M.A., Huber, T. Vollenweider, F.X. (2004), *'Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose – effect study.'* Psychopharmacology, [online] 172(2), pp. 145–156.
Herman, A. (2019), *'Probiotics supplementation in prophylaxis and treatment of depressive and anxiety disorders – review of current research.'* Psychiatria Polska, 53(2), pp. 459–473.
Hett, D., Rogers, J., Humpston, C., Marwaha, S. (2021), *'Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Depression in Adolescence: A Systematic Review.'* Journal of Affective Disorders, 278, pp. 460–469.
Hilber, P., Chapillon, P. (2005), *'Effects of harmaline on anxiety-related behavior in mice.'* Physiology & Behavior, 86(1-2), pp. 164–167.
Hirschfeld, T., Schmidt, T.T. (2021), *'Dose–response relationships of psilocybin-induced subjective experiences in humans.'* Journal of Psychopharmacology, 35(4), p.026988112199267.
Holtzheimer, P.E., McDonald, W. (2014), *'A Clinical Guide to Transcranial Magnetic Stimulation.'* Oxford University Press.
Huang, Y.-Z., Edwards, M.J., Rounis, E., Bhatia, K.P., Rothwell, J.C. (2005), *'Theta Burst Stimulation of the Human Motor Cortex.'* Neuron, 45(2), pp. 201–206.
Janicak, P.G., O'Reardon, J.P., Sampson, S., Husain, M.M., Lisanby, S.H., Rado, J.T., Heart, K. and Demitrack, M.A. (2008), *'Transcranial Magnetic Stimulation in the Treatment of Major Depressive Disorder.'* 69(2), pp. 222–232.
Johnson, M.W., Griffiths, R.R., Hendricks, P.S. Henningfield, J.E. (2018), *'The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act.'* Neuropharmacology, [online] 142(142), pp. 143–166.
Kalfas, M., Taylor, R.H., Dimosthenis Tsapekos, Young, A.H. (2023), *'Psychedelics for treatment resistant depression: are they game changers?'* Expert Opinion on Pharmacotherapy.
Kandola, A., Ashdown-Franks, G., Hendrikse, J., Sabiston, C.M., Stubbs, B. (2019), *'Physical activity and depression: Towards understanding the antidepressant mechanisms of physical activity.'* Neuroscience & Biobehavioral Reviews, [online] 107(0149-7634), pp. 525–539.
Kast, E. (1967), *'Attenuation of anticipation: A therapeutic use of lysergic acid diethylamide.'* The Psychiatric Quarterly, 41(4), pp. 646–657.
Kast, E. (1967), *'Attenuation of anticipation: A therapeutic use of lysergic acid diethylamide.'* The Psychiatric Quarterly, 41(4), pp. 646–657.
Kellner, C.H., Greenberg, R.M., Murrough, J.W., Bryson, E.O., Briggs, M.C. Pasculli, R.M. (2012), *'ECT in Treatment-Resistant Depression.'* American Journal of Psychiatry, 169(12), pp. 1238–1244.
Kim, J., Park, H., Yu, S., Jee, S., Cheon, K., Song, D.H., Kim, S.J., Im, W., Kang, J. (2016), *'Effects of high-frequency repetitive transcranial magnetic stimulation (rTMS) on spontaneously hypertensive rats, an animal model of attention-deficit/hyperactivity disorder.'* International Journal of Developmental Neuroscience, 53(1), pp. 83–89.
Kirov, G., Jauhar, S., Sienaert, P., Kellner, C.H., McLoughlin, D.M. (2021), *'Electroconvulsive therapy for depression: 80 years of progress.'* The British Journal of Psychiatry, 219(5), pp. 1–4.
Kosel, M., Brockmann, H., Frick, C., Zobel, A. Schlaepfer, T.E. (2011), *'Chronic vagus nerve stimulation for treatment-resistant depression increases regional cerebral blood flow in the dorsolateral prefrontal cortex.'* Psychiatry Research: Neuroimaging, 191(3), pp. 153–159.
Koutsomitros, T., Evagorou, O., Schuhmann, T., Zamar, A. and Sack, A.T. (2021), *'Advances in transcranial magnetic stimulation (TMS) and its applications in resistant depression.'* Psychiatriki, 32(Supplement 1), pp. 90–98.

Kraehenmann, R., Schmidt, A., Friston, K., Preller, K.H., Seifritz, E. Vollenweider, F.X. (2016), *'The mixed serotonin receptor agonist psilocybin reduces threat-induced modulation of amygdala connectivity.'* NeuroImage: Clinical, 11, pp. 53–60.

Kraus, T., Hösl, K., Kiess, O., Schanze, A., Kornhuber, J., Forster, C. (2007), *'Bold fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation.'* Journal of Neural Transmission, 114(11), pp. 1485–1493.

Krauss, J.K., Lipsman, N., Aziz, T., Boutet, A., Brown, P., Chang, J.W., Davidson, B., Grill, W.M., Hariz, M.I., Horn, A., Schulder, M., Mammis, A., Tass, P.A., Volkmann, J. Lozano, A.M. (2020), *'Technology of deep brain stimulation: current status and future directions.'* Nature Reviews Neurology, [online] 17(2), pp. 1–13.

Leiknes, K.A., Schweder, L.J., Høie, B. (2012), *'Contemporary use and practice of electroconvulsive therapy worldwide.'* Brain and Behavior, 2(3), pp. 283–344.

Lex, H., Nevers, S.W., Jensen, E.L., Ginsburg, Y., Maixner, D.F., Mickey, B.J. (2021), *'Long-term quality of life in treatment-resistant depression after electroconvulsive therapy.'* Journal of Affective Disorders, 291, pp. 135–139.

Li, H., Cui, L., Li, J., Liu, Y. Chen, Y. (2021), *'Comparative efficacy and acceptability of neuromodulation procedures in the treatment of treatment-resistant depression: a network meta-analysis of randomized controlled trials.'* Journal of Affective Disorders, 287, pp. 115–124.

Li, N.-X., Hu, Y.-R., Chen, W.-N. Zhang, B. (2022), *'Dose effect of Psilocybin on Primary and Secondary Depression: A preliminary systematic review and meta-analysis.'* Journal of Affective Disorders, 296(1), pp. 26–34.

Li, Z., Liu, S., Wang, L., Smith, L. (2019), *'Mind-Body Exercise for Anxiety and Depression in COPD Patients: A Systematic Review and Meta-Analysis.'* International Journal of Environmental Research and Public Health, 17(1), p. 22.

Lin, I-Hui., Huang, C.-Y., Chou, S.-H., Shih, C.-L. (2022), *'Efficacy of Prenatal Yoga in the Treatment of Depression and Anxiety during Pregnancy: A Systematic Review and Meta-Analysis.'* International Journal of Environmental Research and Public Health, 19(9), p. 5368.

Liu, R.T., Walsh, R.F.L., Sheehan, A.E. (2019) *'Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials.'* Neuroscience & Biobehavioral Reviews, 102, pp. 13–23.

Machado-Vieira, R., Baumann, J., Wheeler-Castillo, C., Latov, D., Henter, I., Salvadore, G., Zarate, C. (2010), *'The Timing of Antidepressant Effects: A Comparison of Diverse Pharmacological and Somatic Treatments.'* Pharmaceuticals, [online] 3(1), pp. 19–41.

Madsen, M.K., Fisher, P.M., Burmester, D., Dyssegaard, A., Stenbæk, D.S., Kristiansen, S., Johansen, S.S., Lehel, S., Linnet, K., Svarer, C., Erritzoe, D., Ozenne, B., Knudsen, G.M. (2019), *'Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels.'* Neuropsychopharmacology, [online] 44(7), pp. 1328–1334.

Mayberg, H.S., Lozano, A.M., Voon, V., McNeely, H.E., Seminowicz, D., Hamani, C., Schwalb, J.M., Kennedy, S.H. (2005), *'Deep Brain Stimulation for Treatment-Resistant Depression.'* Neuron, [online] 45(5), pp. 651–660.

Mehta, S., Downar, J., Mulsant, B.H., Voineskos, D., Daskalakis, Z.J., Weissman, C.R., Vila-Rodriguez, F., Blumberger, D.M. (2022), *'The Effect of High Frequency Versus Theta-Burst Repetitive Transcranial Magnetic Stimulation on Suicidality in Patients with Treatment Resistant Depression.'* Acta Psychiatrica Scandinavica.

Minayo, M. de S., Miranda, I., Telhado, R.S. (2021), *'Revisão sistemática sobre os efeitos dos probióticos na depressão e ansiedade: terapêutica alternativa?'* Ciência & Saúde Coletiva, [online] 26, pp. 4087–4099.

Moncrieff, J., Cooper, R.E., Stockmann, T., Amendola, S., Hengartner, M.P., Horowitz,

M.A. (2022), *'The Serotonin Theory of depression: a Systematic Umbrella Review of the Evidence.'* Molecular Psychiatry, [online] 28(3243–3256), pp. 1–14.

Muttoni, S., Ardissino, M., John, C. (2019), *'Classical psychedelics for the treatment of depression and anxiety: A systematic review.'* Journal of Affective Disorders, 258(1), pp. 11–24.

Nichols, D.E. (2016), *'Psychedelics.'* Pharmacological Reviews. 68(2), pp. 264–355.

O'Reardon, J.P., Cristancho, P., Peshek, A.D. (2006), *'Vagus nerve stimulation (VNS) and treatment of depression: to the brainstem and beyond.'* PubMed [Preprint]. https://pubmed.ncbi.nlm.nih.gov/21103178.

Olano, FJA & Rosenbaum B (2022), *'Short-term psychodynamic psychotherapy.'* Ugeskrift for Laeger, vol. 184, no. 27.

Osório, F. de L., Sanches, R.F., Macedo, L.R., dos Santos, R.G., Maia-de-Oliveira, J.P., Wichert-Ana, L., de Araujo, D.B., Riba, J., Crippa, J.A., Hallak, J.E. (2015), *'Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report.'* Revista Brasileira de Psiquiatria, 37(1), pp. 13–20.

Pandey, G.N., Dwivedi, Y., Rizavi, H.S., Ren, X., Pandey, S.C., Pesold, C., Roberts, R.C., Conley, R.R., Tamminga, C.A. (2002), *'Higher Expression of Serotonin 5-HT2A Receptors in the Postmortem Brains of Teenage Suicide Victims.'* American Journal of Psychiatry, 159(3), pp. 419–429.

Passie, T., Halpern, J.H., Stichtenoth, D.O., Emrich, H.M. and Hintzen, A. (2008), *'The Pharmacology of Lysergic Acid Diethylamide: A Review.'* CNS Neuroscience & Therapeutics, 14(4), pp. 295–314.

Passie, T., Halpern, J.H., Stichtenoth, D.O., Emrich, H.M. Hintzen, A. (2008) *'The Pharmacology of Lysergic Acid Diethylamide: A Review.'* CNS Neuroscience & Therapeutics, 14(4), pp. 295–314.

Pearce, M., Garcia, L., Abbas, A., Strain, T., Schuch, F.B., Golubic, R., Kelly, P., Khan, S., Utukuri, M., Laird, Y., Mok, A., Smith, A., Tainio, M., Brage, S., Woodcock, J. (2022), *'Association Between Physical Activity and Risk of Depression: A Systematic Review and Meta-analysis.'* Jama psychiatry, [online] 79(6).

Perez, N., Langlest, F., Mallet, L., De Pieri, M., Sentissi, O., Thorens, G., Seragnoli, F., Zullino, D., Kirschner, M., Kaiser, S., Solmi, M., Sabé, M. (2023), *'Psilocybin-assisted therapy for depression: A systematic review and dose-response meta-analysis of human studies.'* European Neuropsychopharmacology, [online] 76, pp. 61–76.

Peuker, E.T. and Filler, T.J. (2002), *'The nerve supply of the human auricle.'* Clinical Anatomy, 15(1), pp. 35–37.

Porcelan, J, Scribner, K & Gentile, JP (2022), *'Brief Psychodynamic Psychotherapy: A Review and Illustrative Case Vignette.'* Innovations in Clinical Neuroscience, vol. 19, no. 1-3, pp. 52–55.

Powell, V.B., Abreu, N., Oliveira, I.R. de, Sudak, D. (2008), *'Terapia cognitivo-comportamental da depressão.'* Revista Brasileira de Psiquiatria, [online] 30(suppl 2), pp. s73–s80.

Rankaduwa, S. Owen, A.M. (2023), *'Psychedelics, entropic brain theory, and the taxonomy of conscious states: a summary of debates and perspectives.'* Neuroscience of Consciousness, 2023(1).

Riba, J., Rodríguez-Fornells, A., Urbano, G., Morte, A., Antonijoan, R., Montero, M., Callaway, J.C., Barbanoj, M.J. (2001), *'Subjective effects and tolerability of the South American psychoactive beverage Ayahuasca in healthy volunteers.'* Psychopharmacology, 154(1), pp. 85–95.

Richards, D. (2011), *'Prevalence and clinical course of depression: A review.'* Clinical Psychology Review, 31(7), pp. 1117–1125.

Richards, W.A., Rhead, J.C., Dileo, F.B., Yensen, R., Kurland, A.A. (1977), *'The Peak Experience Variable in DPT-Assisted Psychotherapy with Cancer Patients.'* Journal of Psychedelic Drugs, 9(1), pp. 1–10.

Richards, W.A., Rhead, J.C., Dileo, F.B., Yensen, R., Kurland, A.A. (1977), *'The Peak Experience Variable in DPT-Assisted Psychotherapy with Cancer Patients.'* Journal of Psychedelic Drugs, 9(1), pp. 1–10.

Rickli, A., Moning, O.D., Hoener, M.C. Liechti, M.E. (2016), *'Receptor interaction profiles of novel psychoactive tryptamines compared with classic hallucinogens.'* European Neuropsychopharmacology, 26(8), pp. 1327–1337.

Rosenquist, P.B., Youssef, N.A., Surya, S. and McCall, W.V. (2018), *'When All Else Fails: The Use of Electroconvulsive Therapy for Conditions Other than Major Depressive Episode.'* Psychiatric Clinics, [online] 41(3), pp. 355–371.

Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., Carpenter, L.L., Cincotta, M., Chen, R., Daskalakis, J.D., Di Lazzaro, V., Fox, M.D., George, M.S., Gilbert, D., Kimiskidis, V.K., Koch, G., Ilmoniemi, R.J., Lefaucheur, J.P., Leocani, L., Lisanby, S.H. (2021), *'Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines.'* Clinical Neurophysiology, 132(1), pp. 269–306.

Rush, A.J., Marangell, L.B., Sackeim, H.A., George, M.S., Brannan, S.K., Davis, S.M., Howland, R., Kling, M.A., Rittberg, B.R., Burke, W.J., Rapaport, M.H., Zajecka, J., Nierenberg, A.A., Husain, M.M., Ginsberg, D., Cooke, R.G. (2005), *'Vagus Nerve Stimulation for Treatment-Resistant Depression: A Randomized, Controlled Acute Phase Trial.'* Biological Psychiatry, 58(5), pp. 347–354.

Santos, R.G., Landeira-Fernandez, J., Strassman, R.J., Motta, V., Cruz, A.P.M. (2007), *'Effects of ayahuasca on psychometric measures of anxiety, panic-like and hopelessness in Santo Daime members.'* Journal of Ethnopharmacology, 112(3), pp. 507–513.

Saran, T., Mazur, A., Łukasiewicz, J. (2021), *'The significance of physical activity in the prevention of depressive disorders.'* Psychiatria Polska, 55(5), pp. 1025–1046.

Shelton, R.C., Sanders-Bush, E., Manier, D.H. Lewis, D.A. (2009), *'Elevated 5-HT 2A receptors in postmortem prefrontal cortex in major depression is associated with reduced activity of protein kinase A.'* Neuroscience, 158(4), pp.1406–1415.

Sherrard, R.M., Morellini, N., Jourdan, N., El-Esawi, M., Arthaut, L.-D., Niessner, C., Rouyer, F., Klarsfeld, A., Doulazmi, M., Witczak, J., d'Harlingue, A., Mariani, J., Mclure, I., Martino, C.F., Ahmad, M. (2018), *'Low-intensity electromagnetic fields induce human cryptochrome to modulate intracellular reactive oxygen species.'* Plos biology, 16(10), p. E2006229.

sladky, R., Spies, M., Hoffmann, A., Kranz, G., Hummer, A., Gryglewski, G., Lanzenberger, R., Windischberger, C., Kasper, S. (2015), *'(S)-citalopram influences amygdala modulation in healthy subjects: a randomized placebo-controlled double-blind fMRI study using dynamic causal modeling.'* NeuroImage, 108, pp. 243–250.

Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J.B., Jones, P., Kim, J.H., Kim, J.Y., Carvalho, A.F., Seeman, M.V., Correll, C.U. Fusar-Poli, P. (2022), *'Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies.'* Molecular Psychiatry, [online] 27(1), pp. 281–295.

Spitz, N.A., Ten Eyck, P., Nizar, K., Boes, A.D. and Trapp, N.T. (2022), *'Similar Outcomes in Treating Major Depressive Disorder With 10 Hz Repetitive Transcranial Magnetic Stimulation (rTMS) Versus Intermittent Theta Burst Stimulation (iTBS): A Naturalistic Observational Study.'* Journal of Psychiatric Practice, 28(2), pp. 98–107.

Stoliker, D., Egan, G.F., Friston, K.J. and Razi, A. (2022), *'Neural Mechanisms and Psychology of Psychedelic Ego Dissolution.'* Pharmacological Reviews, 74(4), pp. 876–917.

Studerus, E., Kometer, M., Hasler, F., Vollenweider, F.X. (2011), *'Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies.'* Journal of Psychopharmacology, 25(11), pp. 1434–1452.

Sudak, D.M. (2012), *'Cognitive Behavioral Therapy for Depression.'* Psychiatric Clinics of North America, [online] 35(1), pp. 99–110.

T. Dufor, Grehl, S., Tang, A.D., M. Doulazmi, M. Traoré, Debray, N., C. Dubacq, Deng, Z.-D., Mariani, J., Lohof, A.M., Sherrard, R.M.

(2019), *'Neural circuit repair by low-intensity magnetic stimulation requires cellular magnetoreceptors and specific stimulation patterns.'* Science Advances, 5(10).

Takamiya, A., Chung, J.K., Liang, K.-C., Graff-Guerrero, A., Mimura, M., Kishimoto, T. (2018), *'Effect of electroconvulsive therapy on hippocampal and amygdala volumes: systematic review and meta-analysis.'* The British Journal of Psychiatry: The Journal of Mental Science, [online] 212(1), pp. 19–26.

Tan, C., Qiao, M., Ma, Y., Luo, Y., Fang, J., Yang, Y. (2023), *'The efficacy and safety of transcutaneous auricular vagus nerve stimulation in the treatment of depressive disorder: A systematic review and meta-analysis of randomized controlled trials.'* Journal of Affective Disorders, [online] 337, pp. 37–49.

Thirthalli, J., Naik, S.S., Kunigiri, G. (2020), *'Frequency and Duration of Course of ECT Sessions: An Appraisal of Recent Evidence.'* Indian Journal of Psychological Medicine, [online] 42(3), pp. 207–218.

Tylee, A., Walters, P. (2007), *'Onset of action of antidepressants.'* BMJ, 334(7600), pp. 911–912.

Ulloa, L. (2021), *'Electroacupuncture activates neurons to switch off inflammation.'* Nature.

Vaidya, V.A., Marek, G.J., Aghajanian, G.K. and Duman, R.S. (1997), *'5-HT2A Receptor-Mediated Regulation of Brain-Derived Neurotrophic Factor mRNA in the Hippocampus and the Neocortex.'* Journal of Neuroscience, [online] 17(8), pp. 2785–2795.

van Diermen, L., van den Ameele, S., Kamperman, A.M., Sabbe, B.C.G., Vermeulen, T., Schrijvers, D., Birkenhäger, T.K. (2018), *'Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis.'* The British Journal of Psychiatry, 212(2), pp. 71–80.

Vargas, M.V., Dunlap, L.E., Dong, C., Carter, S.J., Tombari, R.J., Jami, S.A., Cameron, L.P., Patel, S.D., Hennessey, J.J., Saeger, H.N., McCorvy, J.D., Gray, J.A., Tian, L., Olson, D.E. (2023), *'Psychedelics promote neuroplasticity through the activation of intracellular 5-HT2A receptors.'* Science, 379(6633), pp. 700–706.

Ventureyra, E.C.G. (2000), *'Transcutaneous vagus nerve stimulation for partial onset seizure therapy.'* Child's Nervous System, 16(2), pp. 101–102.

Vollenweider, F.X., Vollenweider-Scherpenhuyzen, M.F.I., Bäbler, A., Vogel, H., Hell, D. (1998), *'Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action.'* NeuroReport, 9(17), pp. 3897–3902.

Wang, M., Liu, W., Ge, J., Liu, S. (2023), *'The immunomodulatory mechanisms for acupuncture practice.'* Frontiers in Immunology, [online] 14.

Wienicke, F.J., Beutel, M.E., Zwerenz, R., Brähler, E., Fonagy, P., Luyten, P., Constantinou, M., Barber, J.P., McCarthy, K.S., Solomonov, N., Cooper, P.J., De Pascalis, L., Johansson, R., Andersson, G., Lemma, A., Town, J.M., Abbass, A.A., Ajilchi, B., Connolly Gibbons, M.B., López-Rodríguez, J. (2023), *'Efficacy and moderators of short-term psychodynamic psychotherapy for depression: A systematic review and meta-analysis of individual participant data.'* Clinical Psychology Review, [online] 101, p. 102269.

Wienicke, F.J., Beutel, M.E., Zwerenz, R., Brähler, E., Fonagy, P., Luyten, P., Constantinou, M., Barber, J.P., McCarthy, K.S., Solomonov, N., Cooper, P.J., De Pascalis, L., Johansson, R., Andersson, G., Lemma, A., Town, J.M., Abbass, A.A., Ajilchi, B., Connolly Gibbons, M.B. López-Rodríguez, J. (2023), *'Efficacy and moderators of short-term psychodynamic psychotherapy for depression: A systematic review and meta-analysis of individual participant data.'* Clinical Psychology Review, [online] 101, p. 102269.

Wilkos, E., Tylec, A., Kulakowska, D., Kucharska, K. (2013), *'Najnowsze kierunki terapeutyczne w rehabilitacji pacjentów z zaburzeniami psychicznymi.'* Psychiatria Polska, 47(4), pp. 621–634.

Yang, N.-N., Lin, L.-L., Li, Y.-J., Li, H.-P., Cao, Y., Tan, C.-X., Hao, X.-W., Ma, S.-M., Wang, L. and Liu, C.-Z. (2021), *'Potential Mechanisms and Clinical Effectiveness of Acupuncture in Depression.'* Current Neuropharmacology, 19.

Youssef, M.M., Underwood, M.D., Huang, Y.-Y., Hsiung, S., Liu, Y., Simpson, N.R., Bakalian, M.J., Rosoklija, G.B., Dwork, A.J., Arango, V.

and Mann, J.J. (2018), *'Association of BDNF Val66Met Polymorphism and Brain BDNF Levels with Major Depression and Suicide.'* International Journal of Neuropsychopharmacology, 21(6), pp. 528–538.

Zhang, A., Borhneimer, L.A., Weaver, A., Franklin, C., Hai, A.H., Guz, S., Shen, L. (2019), *'Cognitive behavioral therapy for primary care depression and anxiety: a secondary meta-analytic review using robust variance estimation in meta-regression.'* Journal of Behavioral Medicine, [online] 42(6), pp. 1117–1141.

Zhang, C., Zhang, Y., Luo, H., Xu, X., Yuan, T., Li, D., Cai, Y., Gong, H., Peng, D., Fang, Y., Voon, V., Sun, B. (2022), *'Bilateral Habenula deep brain stimulation for treatment-resistant depression: clinical findings and electrophysiological features.'* Translational Psychiatry, 12(1).

Zhao, H., Jiang, C., Zhao, M., Ye, Y., Yu, L., Li, Y., Luan, H., Zhang, S., Xu, P., Chen, X., Pan, F., Shang, D., Hu, X., Jin, K., Chen, J., Mou, T., Hu, S., Fitzgibbon, B.M., Fitzgerald, P.B., Cash, R.F.H. (2023), *'Comparisons of Accelerated Continuous and Intermittent Theta Burst Stimulation for Treatment-Resistant Depression and Suicidal Ideation.'* Biological Psychiatry, [online] pp. S0006-3223(23)017882.

Zhu, Z., Hubbard, E., Guo, X., Barbosa, D.A.N., Popal, A.M., Cai, C., Jiang, H., Zheng, Z., Lin, J., Gao, W., Zhang, J., Bartas, K., Macchia, D., Derdeyn, P., Halpern, C.H., Mayberg, H.S., Beier, K.T., Zhu, J., Wu, H. (2021), *'A connectomic analysis of deep brain stimulation for treatment-resistant depression.'* Brain Stimulation, [online] 14(5), pp. 1226–1233.

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