The rise of mental health disorders poses a danger to society globally. Recent emerging evidence suggests psychedelics can be utilised in the treatment of mental illness. Discuss these aspects, with focus on the effects exerted by psychedelics.

Abstract

Psychedelics are a class of drugs known as “hallucinogens” that produce mind altering and distorting effects once taken into the body. Of their countless numbers, psilocybin is the most extensively studied and was shown to have the safest profile. The effects exerted are dependent on several factors including dosage and type of psychedelic. Psilocybin containing mushrooms are very common and are very difficult to differentiate. Increased demand has led to the synthetic production of psilocybin to improve the poor yield currently generated. Research has shown psilocybin’s immense potential in treating major mental disorders such as depression and anxiety. Psilocybin is converted into its active form psilocin mainly in the liver where it enters circulation to reach the brain. The mechanism of action of psychedelics and psilocybin is known to involve the serotonin and dopamine messenger systems which helps explain how it can aid with mood disorders. Magic mushrooms call forth further research as the synergistic effects present between the compounds must be considered and studied further as this unique property distinguishes itself from psilocybin alone. With the increased potential and attractive future of psilocybin, one must remain aware of the possible side effects and limitations present that are preventing the psychedelic industry from advancing even further.

As we enter the modern era, mental health remains one of the most deprived areas of public health. This is evident with WHO's estimation of 1 billion people living with a mental disorder in 2020 [1]. Of those affected, anxiety-related disorders were the most common, affecting 284 million people while depression affected 264 million people globally [1]. To further support this urgency, it was also announced that one person dies every 40 seconds by suicide, contributing to approximately 800,000 deaths per year [1]. With the recent COVID-19 pandemic and the prolonged lockdowns, the global isolation only exacerbated this predicament leading to a further rise in anxiety and depression [1]. This presenting need has been met with limited access to affordable mental health care, only worsened by the pandemic [1]. It is important to note that the presenting stigma regarding seeking mental health treatment remains widespread and prevalent which is contributing to the staggering 75% of undiagnosed mental health conditions in low and middle-income countries [1]. The use of psychedelics in treating mental illness is a wild but interesting concept to research. This was conducted in the 1950s and 1960s and persisted until psychedelics were declared a schedule 1 substance in 1973, rendering its possession even for research illegal [2]. This forced psychedelics and their potential to lay dormant for decades until a 2006 publication, which sparked the new age for psychedelic research and reignited interest globally [2]. This led to the subsequent formation of major centres for research, contributing to 27,000 publications on psychedelic drugs [2]. Psychedelics are hallucinogenic drugs that act to alter your mind and perception once taken [2]. The vast number of psychedelics along with their complicated names create an intimidating environment to venture into, especially as a beginner and as someone who has never heard of this drug class. To allow for a more focused and analytical approach I will be utilising psilocybin as the main point of this paper. It was reported that this psychedelic compound is currently the most studied and contains the safest profile, making it a favourable and attractive option for future treatments [2]. In light of what was mentioned, this essay will go into the mechanism of action of psychedelics before explaining how psilocybin exerts its action in the body. The features of magic mushrooms will be touched upon as well as its distinguishing effects from psilocybin.

Furthermore, any adverse reactions and toxicity will be reported before finally going into the therapeutic potential of psilocybin.

With the introduction of psychedelics as a potential prospect for mental health treatment, it remains vital to elaborate on how exactly psychedelics work in the body and the response produced. As previously mentioned, psychedelics produce cognitive and sensory changes to the body once ingested. These can include anything from: visual effects, mystical experiences, euphoria, joy and altered awareness of time [3]. The intensity and type of effect experienced is controlled by numerous factors. The current personality, emotional stability and expectations of the person are useful predictors for the outcome of the experience [3]. Furthermore, the setting in which the psychedelic is used, and its dosage can often influence the nature of the experience [3]. Once upset people report experiencing adverse effects, commonly known as a “bad trip” which will be discussed in further detail later [3]. Generally, psychedelic drugs mainly react with serotonin receptors $5HT_{2A}$ and $5HT_{1A}$ to a lesser extent which can be extensively found within the brain [3]. Serotonin receptors regulate emotions such as anxiety, aggression, and cognition as well as numerous other processes [2]. Through their activation, glutamate is released which modulates activation of the amygdala resulting in an increased positive mood through the reduced recognition of negative emotions [3]. Psilocybin containing mushrooms come in an array of shapes and sizes as shown in fig.1., from short and thick stems to tall with tiny caps. Fungi containing psilocybin grow in most continents and are comprised of over a 100 species thriving with a grand range of habitats [5]. Being able to differentiate these mushrooms from psilocybin free types requires the skill of an expert in identifying fungus and with an extensive understanding of the species of fungi that normally grow in the area in question [5]. The

Figure 1: Image showing psilocybin containing mushrooms [4]

potential psilocybin contains is becoming more apparent with increasing research being done on numerous fronts. Currently, institutes and centres are researching psilocybin's efficacy in treating depression, anxiety, alcohol dependence and cluster headaches [2]. Chronic pain is also being investigated with a proposed mechanism behind psilocybin's analgesic properties' being its interaction with nociceptive pathways [2]. While considering these therapeutic areas currently being explored along with the massive economic hole they leave in healthcare worldwide, psilocybin presents itself as a promising stone ready to plug in this hole and improve the quality of life for these patients. As a result, it is important to elaborate on the production of psilocybin as well as its proposed mechanism of action.

Psilocybin, like many other drugs is a compound that must be synthesized. Fig.2. shows the conversion of L-tryptophan into psilocybin through a series of chemical reactions in the body, including phosphorylation as the final step. When ingested psilocybin is dephosphorylated to psilocin by alkaline phosphatase, an enzyme in the liver and nonspecific esterase in the intestines [6]. Psilocin is the active form of the prodrug psilocybin [6]. Due to the increase in research recently, the demand for psilocybin has grown exponentially resulting in the market demand being satisfied through synthetic production [2]. Even though the extraction through naturally growing mushrooms is preferred, the issue comes with the yield obtained. Reports show a yield of 0.1-0.2% of dry weight which would not be economically viable for drug research, limiting it to recreational use [2]. Despite new methods for synthetic production being formulated to improve yield of up to 75%, they have proven to be expensive with their requirements [2]. This increased need and the growing competition has positively impacted the advancement in the technology used to produce psilocybin and given enough time this will usher in a new age of optimized

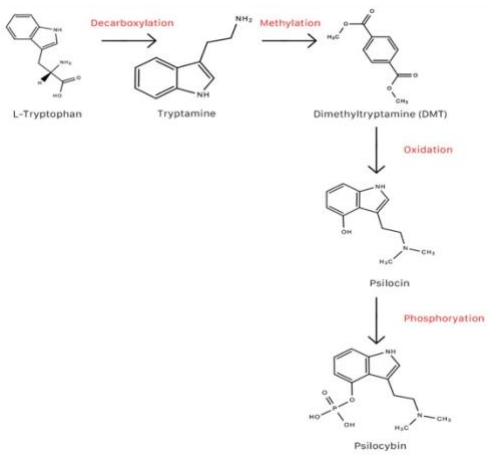

Figure 2: Multistep chemical equation for Psilocybin production [2]

psychedelic production. Regarding psilocin's mechanism of action, it binds to $5HT_{2A}$ and creates a hallucinatory response which mediates its anti-anxiety and antidepressant properties [2]. The medial prefrontal cortex (mPFC) is typically hyperactive during depression, and one antidepressant mechanism psilocin is thought to have is switching off this hyperactivity [2]. Evidence shows psilocybin's indirect interaction with the mesolimbic dopaminergic pathway which plays a major role in the body's reward system [2]. Through this interaction albeit indirect, psilocybin was suggested to exhibit low addictive and abusive properties [2]. Since a positive link was shown between depression and dopamine deficiency in the mesolimbic pathway, psilocybin continues to present itself as a convenient alternative in this medical therapy. In contrast to typical selective serotonin reuptake inhibitors (SSRIs) which can produce anti-depressant effects through dampening the negative emotions created by the amygdala, psilocybin is suggested to produce its anti-depressant effects through increasing positive emotional stimuli in the amygdala [2]. This creates a scenario where one treats their depression not through suppressing the hyperactive pathway but with upregulating the amygdala's reception to positive stimulus. As we cover the action exerted by psilocybin, it is useful to introduce magic mushrooms into the conversation, the effects they produce and how they're different from just psilocybin.

We have been discussing the properties of psilocybin in isolation, but it is important to note the presence of other compounds in magic mushrooms. These compounds function in unison to produce a specific effect. This is an important distinguishing feature from psilocybin alone as the synergism between the multiple compounds found in the mushroom produced a unique effect [2]. The effects vary on several factors such as: the species of mushroom, the person's mindset, mental stability, body type, metabolism, and tolerance level [2]. It can take up to an hour for psychedelic effects to appear after a 2-5g dried dosage and can last between 3 to 6 hours [2]. Some changes produced by magic mushrooms have already been mentioned under the psychedelic umbrella, but other effects shown include reduced suicidal thoughts, changes in outlook, and an improvement of physical and

mental wellbeing [2]. It is important to mention that further research is required with regards to identifying potential synergies between psychoactive compounds and other molecules found in magic mushrooms to reinforce our understanding of how they work to exert their effects. The recommended dose has been argued upon and numerous sources tend to report different dosages depending on a lot of factors such as the mode of administration, tolerance, and body weight [2]. Further research has shown the absence of psilocybin in urine or plasma suggesting increasing dosages will typically not result in any serious physical or psychological effects [2]. After oral administration, most of the psilocybin and its metabolites are processed in the liver as previously mentioned before entering circulation where it will eventually be excreted via the kidneys [2]. It takes about 24 hours for most of the psilocybin and its by-products to be excreted [2]. With a broader understanding of the effects of mushrooms and psilocybin, recognising the adverse effects and risks of overdosing become imperative to effectively weigh the benefits and consequences of the compound as a potential treatment option.

While we begin discussing the associated side effects it is essential to consider the low addictive and abusive properties of psilocybin which was mentioned previously. This does not prevent it from having a high abuse potential due to the experience reported from its use. Furthermore, we have also brought up the term “bad trip”, which is an undesired physical and emotional response including: fear, distress, panic, altered awareness, vomiting, headaches and chills [2]. This is usually treated with benzodiazepines [2]. Mushroom toxicity can also occur resulting in gastroenteritis, rhabdomyolysis, renal failure, and several other complications often requiring medical intervention [2]. With that in mind, psilocybin is reported to have the safest profile of all psychedelics as mentioned and psilocybin overdose is very rare and should carry no worry for most patients unless contraindicated such as those with personal or a family history of psychotic disorders [2]. These patients are discouraged from psilocybin use as it can exacerbate symptoms and worsen their condition. While it is important to remain neutral whilst discussing the efficacy

of a compound as a treatment, it is useful to delve into its therapeutic potential further with focus around its current findings and success in research trials.

For medical professionals to justify the use of psychedelics as a treatment option to the public, the presence of promising results becomes imperative. Extensive research is currently being done on psilocybin's efficacy in alleviating symptoms in major depressive disorder (MDD). The current promising results reinforce the credibility of the anti-depressant properties of psilocybin that was previously listed [7]. One of particular interest was researching the use of psilocybin in patients suffering from life-threatening cancer [8]. Under supportive and controlled conditions, psilocybin was reported to decrease symptoms of depression, anxiety and increased the patients' quality of life [8]. This presents psilocybin as an attractive therapy during palliative care which allows the medical team to alleviate some of the patients suffering and improve their end-of-life care. Psilocybin can further present as a powerful force to curb alcohol dependence. Current research shows a lot of promise in reducing heavy drinking after prolonged psilocybin administration in a safe and controlled manner [9]. One study which included 95 participants found a reduction in how often the psilocybin-assisted group had heavy drinking days when compared to the placebo group [9]. Reports show a 14% reduction in heavy drinking days with psilocybin use for alcohol dependence [9]. With all the increasing support psilocybin and psychedelics as a whole is receiving in the research community it is crucial to note the limitations currently present in the literature. By having a holistic view of research into psychedelics you can begin to have an idea in its current trajectory.

With everything considered the future use of psychedelics as a medical therapy seems inevitable and imminent however, one must keep an open mind regarding the current limitations that need to be overcome to improve this treatment's trust. The yield was an example previously mentioned but others include the lack of larger double-blinded, randomized clinical studies to assess numerous factors of psychedelics with each mood and anxiety disorders [2][10]. This amongst other reasons collectively raise concern amongst

potential investors in this industry. As our technology increases, so does our leniency towards psychedelics as a banned substance as we begin to see more states start decriminalizing and legalizing psychedelics [2]. With further longitudinal and larger research trials we can expand upon the potential this naturally growing mushroom provides and ease this mental burden upon the world one step at a time.

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