Psilocybin as an Abortive Treatment for Intractable Migraines: A Case Report

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Abstract:
Over a billion individuals worldwide suffer from an acute migraine attack in a single year. Approximately 1% of these individuals suffer from status migrainosus, which is defined as a migraine that lasts longer than 72 hours. These chronic intractable migraines are often refractory to conventional treatment interventions. In this case report, the use of the psychedelic agent psilocybin is discussed as an alternative treatment modality for chronic intractable migraines. The pathophysiology of migraines is examined, and the literature on psychedelic substances in treating migraines is reviewed.

INTRODUCTION

Status migrainosus is a migraine that lasts more than 72 hours and often does not respond to typical abortive treatments, and frequently requires emergency department evaluation or inpatient hospitalization for management. Status migrainosus occurs in an estimated one percent of patients who suffer from migraines. Currently, there is no consensus for the treatment of status migrainosus. This case report examines the role of microdosing psilocybin-containing mushrooms in a patient with chronic intractable migraines that are refractory to traditional in-home abortive therapies. A paucity of literature remains regarding psilocybin use in treating migraines despite the discovery of its structural similarity to ergot alkaloids in the early 20th century [1]. Explorations of serotoninergic psychoactive agents, including lysergic acid derivatives and psilocybin, for prophylactic treatment of migraines and cluster headaches, date back to the 1960s [2].

Notably, advancements in genome-wide association studies (GWAS) have shed light on the heterogeneous nature of underlying etiologies. Since these studies were conducted, the underlying pathophysiology of migraines has undergone significant evolution. There has been a shift away from the vascular theory of migraines, which states that vasodilation of cranial vessels is responsible for migraines, and toward a view of migraines as a neurologic disorder with dysfunction in sensory processing [3]. In addition, it has been proposed that conditions like epilepsy, migraines, and affective disorders might share a common pathophysiological mechanism [4]. Other researchers have highlighted the correlation between chronically low serotonin levels in patients with depression and their risk of developing migraines [5]. Furthermore, genetic variability in metal ion homeostasis may also explain migraine susceptibility [6].

It is no surprise, a wide variety of migraine treatments exist with variable outcomes, which leads patients who continue to suffer from persistent symptoms to look for out-of-the-box solutions.

In 2021, a study demonstrated that a single dose of psilocybin in swine models exhibited increased synaptogenesis and expression of neurotrophic factors involved in the maintenance of viability of neurons and neuroplasticity in the hippocampus and prefrontal cortex. Measurable increases in both synaptic protein (SV2A) density and expression of brain-derived neurotrophic factor (BDNF) and Kalirin-7 have also been observed. Psilocybin achieves these results by binding to 5-

Hydroxytryptamine, specifically subset type, 5HT-2A G-protein coupled receptor (GPCR), and subsequent activation of downstream cell signaling pathways [7]. Psilocybin's receptor targets overlap significantly with receptors commonly implicated in the pathogenesis of migraines—specifically, the 5-HT receptors that bind serotonin. The 5-HT2 subtype is of particular note. Psilocybin acts as a partial agonist at the 5-HT2A receptor subtype. Migraine prophylaxis is successfully achieved when the 5-HT2 receptor is blocked by agents such as methysergide, pizotifen, cyproheptadine, or mianserin. However, it should be noted that these agents act on the 5-HT1C subtype, and Ketaserin, a selective 5-HT2 receptor blocker, has yet to demonstrate any efficacy in treating migraines. The underlying pathophysiological mechanism for why modulation of the 5-HT2 receptor improves migraine symptom burden has not been fully elucidated. However, proposed mechanisms include altering cranial vasoconstriction, increased cranial capillary permeability, increased platelet aggregation, or downstream signaling changes in neuroendocrine functions [8].

CASE DESCRIPTION

The patient is a 42-year-old female of Caucasian descent with a past medical history of labyrinthectomy (1982), multiple concussions with loss of consciousness beginning at the age of 5 and later TBI secondary to a motor vehicle accident, cerebrovascular accident (2002), and intractable chronic migraines with status migrainosus starting in 2014, Depressive Disorder Due to Another Medical Condition, generalized anxiety disorder with panic attacks, breast cancer status post radical bilateral mastectomy and chemotherapy on current Tamoxifen therapy. Her family history was notable for depression, anxiety, and OCD in the patient's sister and dementia in two of her grandparents.

Concerning her migraines, triggers primarily included changes in barometric pressure and psychosocial stresses. Other notable migraine symptoms were aura, photosensitivity, a sensation of "teeth itching," and an exacerbation of anxiety symptoms. Her psychotropic medications included Zoloft 100mg PO Daily.

Management and treatment of the patient's migraines included Botox injections every three months, right occipitalis trigger point injections every three months, Glucanezumab-glm 120 mg subcutaneous injection monthly, Cefaly device use 20 minutes daily and an additional 1-hour session weekly, Gabapentin 300 mg PO TID, Magnesium oxide 400 mg PO BID, Riboflavin 100 mg PO QHS. Abortive methods targeted the patient's acute increase in anxiety symptoms during the aura and prodromal phases. These included Hydroxyzine 25 mg PO once as first-line, Lorazepam 1 mg PO once for second line, and Psilocybin ¼ gram for third-line treatment.

The patient did not experience hallucinogenic effects but rather a feeling of being "evened out and smoothing of the rough edges of pain." She denied any notable side effects. Over approximately 15 months, she typically used Psilocybin two times per month. During this period, the patient did experience a 3-day hospitalization for intractable status migrainosus. In contrast, prior to implementing psilocybin in the current regimen, the patient experienced 360 consecutive headache days in 2017 with subsequent hospitalization for uncontrolled pain, severe depression, and suicidal ideation with a plan to overdose on pain medications.

With the improvement in the treatment of her migraine symptoms, the patient has been able to significantly reduce her time away from work resulting in a recent promotion to a management position in quality assurance at her company.

DISCUSSION

Migraines rank as the sixth most common cause of disability globally, with more than one billion patients having an acute migraine episode in any year [9]. Acute migraines cost 19 billion dollars per year in lost wages and productivity, referred to as indirect costs. Annual direct costs of health care estimates, including hospitalizations, outpatient care, and prescriptions, compared migraineurs nearly $23,000 compared with non-migraine affected individuals $16,000 [10]. The current standard of care for the treatment of migraines is highly effective, but 1% of all patients with migraines suffer from intractable migraines in a given year. In this subset of the population of patients who suffer from migraines, alternative or novel treatment modalities are of particular salience. Psychedelic substances, such as psilocybin, have shown remarkable promise in treating difficult to treat or resistant disorders such as Major Depressive Disorder, Post Traumatic Stress Disorder, and Obsessive-Compulsive Disorder [11]. The use of these substances has also been investigated in chronic pain conditions, and results suggest that substances like LSD and Psilocybin may reduce nociceptive and antinociceptive processing through their activity at the 5-HT receptor [12].

Indeed, survey data indicates that psychedelic substances have been effective at treating cluster headaches:

> "The indoleamine hallucinogens, psilocybin, lysergic acid diethylamide, and lysergic acid amide, were comparable to or more efficacious than most conventional medications. These agents were also perceived to shorten/abort a cluster period and bring chronic cluster headaches into remission more than conventional medications. Furthermore, infrequent and non-hallucinogenic doses were reported to be efficacious [13]. "

Further research has also investigated the use of psychedelic substances in both cluster headaches and migraines. Based on self-report measures, the self-treatment, typically with psilocybin or LSD, significantly reduced the frequency and intensity of migraine and cluster headache attacks. In a significant proportion of respondents, full remission of symptoms for both cluster headaches and migraines were also reported. In one study, "Twenty-two of 26 psilocybin users reported that psilocybin aborted attacks; 25 of 48 psilocybin users and 7 of 8 LSD users reported cluster period termination; 18 of 19 psilocybin users and 4 of 5 LSD users reported remission period extension [14]."

A 2021 double-blind, randomized controlled cross-over trial investigated the use of psilocybin vs. placebo in 10 patients with a history of migraines. Patients were given either placebo or Psilocybin (0.143mg/kg) in two treatment sessions two weeks apart. Patients were instructed to keep a headache diary two weeks prior to the trial and continue it until two weeks after the second session. This study showed that psilocybin significantly reduced the number of weekly migraine days and was not correlated with the intensity of acute psychoactive effects during the psychedelic experience. While this study, like most psychedelic studies, has a small sample size, it does signal that there may be a benefit in using these substances in treating refractory migraine symptoms [15].

CONCLUSION:

Psilocybin and other psychedelic substances may provide additional benefits in treating chronic intractable migraines. While the specific pathophysiology causing migraines has not been fully elucidated, modulation of the 5-HT receptor and downstream secondary messaging signaling cascades are likely involved. Psychedelics, specifically serotonergic hallucinogens, exert their effect via

the 5-HT receptors, making them prime candidates for investigation. Preliminary research shows some benefit, especially when compared with placebo-based interventions. However, future research will need to utilize larger sample sizes and compare psychedelic-based substances against the current standard of care medications commonly used in the management of migraine treatment.

AUTHOR INFORMATION

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