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A Novel Therapeutic Approach to Improving Quality of Life and Performance in Athletes and Other Patients with Cluster Headache

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Abstract

Background: Cluster headache (CH) is a rare but severely disabling primary headache disorder characterized by recurrent attacks of excruciating unilateral pain accompanied by cranial autonomic symptoms. Despite the availability of acute and preventive therapies, treatment efficacy remains incomplete and tolerability limitations are common, leaving many athletes and other patients with insufficient symptom control leading to decreased quality of life and performance. Increasing interest has emerged in psychedelic compounds, particularly psilocybin, as potential therapeutic agents in refractory pain conditions, including CH.

Aim: This narrative review aimed to synthesize and critically evaluate the current evidence regarding the efficacy, safety, and potential mechanisms of psilocybin in the treatment of cluster headache.

Material and Methods: A literature search was conducted in the MEDLINE database to identify publications describing psilocybin use in cluster headache. Eligible studies included

clinical trials, retrospective and cross-sectional studies, qualitative analyses, case series, and related observational reports. Eight relevant publications were identified, comprising two clinical studies and six observational investigations.

Results: Clinical evidence remains limited but suggests potential therapeutic benefit. A randomized placebo-controlled trial demonstrated numerically higher response rates with psilocybin compared to placebo, although statistical significance was not achieved, likely due to small sample size. An open-label study reported a mean reduction in attack frequency and identified changes in hypothalamic–diencephalic functional connectivity associated with clinical improvement. Observational studies consistently reported high patient-perceived efficacy for both abortive and preventive use, including attack termination, reduced attack frequency, and prolonged remission periods, often exceeding satisfaction reported with conventional therapies. However, interpretation is limited by methodological constraints including recall bias, selection bias, uncontrolled dosing, diagnostic uncertainty, placebo effects, and the natural episodic course of CH. Available data suggest a generally favorable safety profile under controlled conditions, though psychological adverse effects may occur and long-term safety remains uncertain.

Conclusions: Current evidence indicates a signal of therapeutic potential for psilocybin in cluster headache, particularly in preventive treatment, but remains insufficient for definitive clinical conclusions. Well-designed randomized controlled trials with standardized protocols are urgently needed to clarify efficacy, safety, and optimal therapeutic frameworks for this underserved patient population.

Key words: *CH, cluster headache, headache, psilocybin, classic psychedelics, athletes*

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1. Introduction

Cluster headache (CH) is a primary headache disorder classified among the trigeminal autonomic cephalalgias according to the International Headache Society [1]. It represents the most common entity within this group [2]. CH is characterized by strictly unilateral attacks of severe head and facial pain, most typically localized to the orbital, retro-orbital, or frontotemporal regions [3]. Attacks reach maximum intensity rapidly and may subside just as quickly [1]. The duration of a single episode ranges from 15 to 180 minutes, and attack frequency varies from one every two days up to eight per day [3]. A hallmark of the disorder is its circadian and circannual rhythmicity, with attacks frequently occurring at the same time each day and clustering particularly in spring and autumn [1,4].

The pain experienced during cluster attacks is described as one of the most severe pains known to humans, often rated as worse than childbirth or gunshot wounds [2,4]. Attacks are accompanied by ipsilateral cranial autonomic symptoms such as lacrimation, rhinorrhea, sinus congestion, and ptosis [3], as well as marked physical agitation or restlessness [1]. The syndrome has been referred to as an “alarm-clock headache” due to its striking periodicity [5]. Clinically, two forms are distinguished: episodic CH, accounting for approximately 90% of cases and characterized by bouts lasting weeks to months followed by remission, and chronic CH, in which remissions are absent or short-lived [1].

The lifetime prevalence of CH is estimated at approximately 0.05–0.1% [3] or 1.24 per 1000 individuals. The typical age of onset is between 20 and 40 years [2]. The disorder is more common in men, with reported male-to-female ratios ranging from 2:1 to 6:1 [1,3]. Beyond

pain, CH profoundly affects quality of life. A substantial proportion of patients report significant restriction in everyday functioning, both during active bouts and even in remission periods, underscoring its chronically disabling nature [2]. For athletes, it may additionally impair training consistency, physical performance, and competitive outcomes, further amplifying the overall burden of the disorder [6,7,8,9].

The etiology of CH is complex and not fully elucidated. Historically, it was considered primarily a vascular disorder; however, vascular mechanisms alone fail to explain its circadian rhythmicity [4]. Increasing evidence points toward a central role of the hypothalamus, which regulates circadian rhythms and autonomic functions. Both anterior and posterior hypothalamic regions may contribute to the clinical phenotype [5]. In addition, dysfunction of the trigeminal vascular pathway is suggested by the pulsating quality of pain and responsiveness to vasoconstrictive agents. Current evidence therefore supports a model involving both neural and vascular abnormalities, possibly mediated by molecules such as nitric oxide [4].

Acute treatment of cluster attacks relies mainly on subcutaneous sumatriptan and high-flow oxygen [1]. A 6 mg subcutaneous dose of sumatriptan has been shown to be effective in approximately 74–75% of patients [2], while oxygen inhalation at high flow rates is effective in up to 60% [1]. Nevertheless, the high frequency of daily attacks may necessitate repeated use of triptans, raising concerns about excessive or off-label dosing [2]. Preventive therapy is particularly challenging. Verapamil, supported by the strongest evidence, and lithium are commonly used [1], yet only a proportion of patients achieve meaningful reduction in attack frequency. Both agents are associated with significant adverse effects and contraindications, leading many patients to discontinue treatment within months [2]. Corticosteroids may be used as bridging therapy but also carry substantial side-effect burdens [1].

Taken together, although several pharmacological options exist, their efficacy is incomplete, tolerability is limited, and accessibility may be restricted in certain healthcare systems [1]. For many individuals, cluster headache remains a profoundly disabling and excruciating condition with insufficiently satisfactory therapeutic control, standing as one of the most devastating pain syndromes in clinical medicine. Faced with recurrent attacks of extreme intensity and limited long-term relief, patients may feel compelled to seek alternative or unconventional therapeutic strategies, including the use of illicit substances such as psychedelics [2].

Psychedelics are a class of hallucinogenic substances that produce profound alterations in perception, cognition, and the sense of reality after ingestion. These mind-altering effects may include hallucinations, emotional fluctuations, delusional thinking, and experiences of detachment or derealization [10]. Within this broad group, classic (serotonergic) agents such

as lysergic acid diethylamide (LSD) and psilocybin are distinguished from dissociative psychedelics such as ketamine [11]. From a pharmacological perspective, classic psychedelics exert their psychoactive action primarily through interaction with 5-hydroxytryptamine (5-HT) receptors and their subtypes, which are widely distributed in the central and peripheral nervous systems and are involved in regulating mood, cognition, learning, memory, appetite, and other neuropsychiatric and biological processes [10].

After decades of limited clinical research, interest in the therapeutic applications of psychedelics has markedly resurged over the past two decades. Contemporary investigations have explored their potential role in a variety of medical disorders, extending beyond their well-known subjective effects, which are often described as mystical or spiritual experiences characterized by feelings of unity, sacredness, and transcendence [12]. In particular, psychedelics have recently gained attention as promising agents in the management of pain syndromes. Evidence suggests that these compounds may modulate both the sensory and affective dimensions of pain, with reported benefits in palliative care [11]. Much of the earlier literature focused on patients with terminal cancer, but beneficial effects have also been described in other painful conditions [3]. Case series, surveys, and open-label studies have further described analgesic effects of psychedelics in phantom limb pain, migraine, gangrene, herpes zoster, low back pain and cluster headache [12]. Across these reports, both acute and preventive effects were observed, suggesting the possibility of sustained therapeutic benefit [3].

Among the various compounds within this class, psilocybin has attracted particular attention. Psilocybin is a naturally occurring indoleamine hallucinogen found in approximately 100 species of mushrooms belonging to the genus Psilocybe. It functions as a prodrug that is dephosphorylated into its active metabolite, psilocin, by alkaline phosphatase in the liver and intestinal mucosa esterases [11]. Historically, psilocybin-containing mushrooms have been used for thousands of years in ceremonial and spiritual contexts, and in modern times they are widely recognized for recreational use. Beyond these uses, accumulating anecdotal and scientific evidence points to significant medicinal value. Although direct comparative studies between different psychedelic agents are lacking, the substantial body of evidence available for psilocybin alone suggests that it may be among the most efficacious compounds within this class for certain disorders [10].

In pain medicine, psilocybin has demonstrated particular promise. A systematic review of eight studies supported its analgesic potential in migraine treatment [11], and the first clinical trial of a psychedelic drug in migraine showed that a single low dose of psilocybin reduced weekly migraine days and pain intensity over a two-week period in episodic cases [13]. Case reports

and qualitative studies have also suggested possible benefit in neuropathic pain [11]. Furthermore, psilocybin has demonstrated analgesic effects in chronic pain states, including intractable phantom pain [10]. These findings, together with its documented antidepressant and anxiolytic properties—which may provide additional benefit to patients with comorbid mood or anxiety symptoms frequently accompanying chronic pain [12]—have positioned psilocybin as a particularly compelling candidate for further investigation.

The therapeutic effects of psychedelics in headache disorders have been recognized for decades, and controlled studies are now beginning to emerge [13]. In cluster headache specifically, the severe nature of attacks and limited availability of effective therapies led patients in the 1990s to experiment with classic psychedelic compounds as a means of disease management [3]. Given psilocybin's historical use, pharmacological profile, and emerging evidence of efficacy across multiple pain syndromes, researchers in recent years have increasingly sought to evaluate its potential role in cluster headache.

While narrative and systematic reviews addressing the efficacy of various psychedelics in cluster headache are already available, a review dedicated exclusively to psilocybin in this condition has not yet been conducted. In light of its unique clinical profile and accumulating evidence base, we therefore undertook a focused narrative review to synthesize the existing literature on psilocybin in cluster headache.

2. Material and methods

We carried out a literature search in MEDLINE database. We searched for all publications in which the usage of psilocybin on cluster headache was described. Publications of case reports, case series, retrospective studies, qualitative analyses, systematic reviews as well as uncontrolled and controlled clinical studies were included. The reference list was manually inspected to identify further relevant publications. Out of 36 results we found only 8 relevant publications which constituted 2 clinical studies, 1 cross-sectional studies, 1 qualitative analysis and 4 retrospective observational studies.

3. Results

3.1. Clinical studies

Two prospective clinical investigations evaluated the effects of psilocybin in patients with cluster headache under structured conditions.

In the exploratory randomized, double-blind, placebo-controlled trial conducted by Schindler et al., 14 participants were randomized to psilocybin or placebo, stratified by headache subtype, and followed using detailed headache diaries. Across thresholds of ≥25%, ≥50%, and ≥75% reduction in weekly attack frequency, numerically higher response rates were observed in the psilocybin group compared to placebo (e.g., 50% vs. 33.3% achieving ≥25% reduction; 37.5% vs. 33.3% achieving ≥50% reduction). However, none of the participants in either group achieved a 100% reduction, and between-group differences did not reach statistical significance, likely due to the small sample size. No significant differences were found in attack duration or pain severity between psilocybin and placebo [14].

In contrast, the open-label trial by Madsen et al., which included 10 patients with chronic cluster headache, demonstrated a mean 31% reduction in attack frequency from baseline to follow-up after three peroral doses of psilocybin. One participant experienced a prolonged complete remission lasting 21 weeks. The treatment was reported as well tolerated. Importantly, changes in hypothalamic–diencephalic functional connectivity correlated negatively with percentage change in attack frequency, suggesting a potential neurobiological correlate of treatment response [15].

Taken together, while the randomized trial did not show statistically significant superiority over placebo, the open-label study suggested clinically meaningful reductions in attack frequency and possible mechanistic involvement of hypothalamic networks [14,15].

3.2. Observational studies

Across observational designs—including surveys, cross-sectional studies, and qualitative analyses—psilocybin was frequently reported as beneficial, particularly in patients dissatisfied with conventional therapies.

In the survey by Sewell et al., which included 53 individuals with cluster headache, psilocybin was reported as effective both abortively and prophylactically. Among episodic cluster headache patients who used sublingual psilocybin during attacks, 17 of 19 reported successful abortion within 20 minutes. Prophylactically, 52% reported complete cessation of attacks and 41% partial efficacy. Additionally, 19 of 20 individuals who used psilocybin during remission reported prolongation of their remission period. In chronic cluster headache, 5 of 7 reported successful abortive effects, and 10 of 20 reported complete termination of attacks, with a further 8 reporting partial benefit. Notably, efficacy was observed even with subhallucinogenic doses, suggesting that therapeutic effects may be independent of psychoactive intensity [16].

This aligns with the broader survey by Schindler et al., which analyzed 496 validated responders. In abortive treatment comparisons, psilocybin was reported as less effective than triptan injections but significantly more effective than oral and intranasal triptans. For preventive treatment, psilocybin was reported as significantly more effective than verapamil and prednisone. In free-text responses regarding remission from chronic cluster headache, psilocybin was the most frequently cited agent (30.0%), and it was also the most prevalent response when respondents were asked what shortened or aborted a cluster period (33.7%) [17].
The 2024 questionnaire study by Smedfors et al. further contextualized these findings within overall treatment satisfaction. While 46.5% of respondents were satisfied with abortive therapy and 27.4% with preventive therapy, conventional first-line preventive agents such as verapamil yielded full effect in only 10.5% of users. Among those who had tried psilocybin for prevention, 58.3% reported full preventive effect and 91.7% reported at least some degree of effect (full, moderate, or partial). For abortive use, all eight individuals who reported using psilocybin experienced either full or partial attack abortion [18]. Similarly, in the online survey by Di Lorenzo et al., all 54 respondents reported dissatisfaction with conventional treatments, and among the 18 who used psilocybin prophylactically, 14 described full or partial efficacy [19].
The cross-sectional study by de Coo et al. demonstrated that individuals with cluster headache reported higher illicit drug use compared to the general population with headache or chronic pain. Among those using illicit substances during cluster episodes, 56.4% reported decreased attack frequency with psilocybin, and 46.2% reported decreased attack duration. These findings suggest that perceived benefit may be specific to cluster headache rather than reflecting a generalized pattern seen in other pain conditions [20].
Finally, qualitative thematic analysis of online forum discussions by Andersson et al. revealed that psilocybin was commonly used according to structured self-treatment regimens such as “busting” or microdosing. Users frequently emphasized prophylactic as well as acute benefits, often aiming to minimize psychoactive effects. Although some individuals reported lack of benefit, these cases were typically associated with uncertainty regarding dosing or limited treatment exposure. Overall, psilocybin was described as highly effective for both prevention and acute management [21].

3.3. **Summary**

In summary, while controlled clinical data remain limited and inconclusive regarding superiority over placebo [14], open-label evidence suggests reductions in attack frequency and

possible neurobiological mechanisms [15]. Observational studies consistently report high rates of perceived efficacy—both abortive and preventive—often exceeding those of conventional oral therapies and, in preventive contexts, even first-line agents. Across multiple designs, psilocybin was frequently associated with attack termination, remission prolongation, and high patient-reported satisfaction, particularly among individuals dissatisfied with standard treatments [16,17,18,19,20].

4. Discussion

4.1. Limitations

The available evidence investigating psilocybin in cluster headache should be interpreted with caution due to multiple methodological limitations present across both clinical and observational studies. A substantial proportion of the currently available data originates from retrospective surveys and self-reported analyses, which inherently introduce recall bias, as participants may inaccurately remember treatment effects or adverse events, particularly when reporting experiences spanning many years of disease duration [16,17,18]. Furthermore, several studies relied on voluntary participation recruited through online platforms or patient communities, creating a considerable risk of selection bias, as individuals experiencing positive outcomes or actively seeking alternative therapies may have been more likely to participate [16,17,18].

Another important limitation concerns the observational nature of most datasets. Non-randomized and self-selected samples reduce causal inference and limit the ability to distinguish treatment effects from confounding factors [17,21]. In survey-based studies, dosing regimens, purity of substances, and treatment schedules were frequently uncontrolled or unverifiable, preventing reliable dose–response analysis [17,18]. Additionally, diagnostic validity of CH could not always be clinically confirmed, further complicating interpretation of outcomes [17,19].

Placebo effects represent another significant concern. Psychedelic substances are widely discussed within patient communities as highly effective therapies, potentially amplifying expectations and inflating perceived benefit [18]. Psychedelics may additionally enhance suggestibility through psychological mechanisms related to “set and setting,” thereby further strengthening placebo responses [12]. In clinical contexts, psilocybin’s pronounced psychoactive effects may also unintentionally unblind participants despite double-blind designs, potentially influencing subjective outcome reporting [14]

Interpretation of efficacy is further complicated by the natural history of episodic CH. Cluster periods may terminate spontaneously, making it difficult to determine whether improvement reflects therapeutic action or the natural resolution of a bout [2]. Small sample sizes in clinical trials additionally limit statistical power and may explain the absence of significant between-group differences despite numerically favorable outcomes [14].

Sociobehavioral factors may also influence reported outcomes. Evidence suggests that patients with CH demonstrate higher rates of illicit drug use compared with other headache populations, raising the possibility of shared vulnerability toward addictive behaviors [20]. Moreover, illicit substance use sometimes disrupted physician–patient relationships, with some individuals discontinuing medical consultations or losing access to professional care after disclosing psychedelic use, which may have affected treatment trajectories and reporting patterns [19].

Despite these limitations, the overall body of evidence remains noteworthy. Across heterogeneous study designs, psilocybin was repeatedly associated with reductions in attack frequency, termination of cluster periods, or prolongation of remission in patients often refractory to conventional therapies [16,17,18]. The convergence of findings across independent methodologies suggests that the observed effects warrant continued scientific investigation rather than dismissal as solely methodological artifact.

4.2. Possible mechanisms underlying therapeutic effects

Attempts to explain psilocybin's potential efficacy in CH may be grounded in its pharmacological activity within serotonergic systems. Psilocybin is metabolized to psilocin, which acts primarily as an agonist at 5-HT2A receptors widely distributed throughout the central nervous system and involved in pain perception and emotional processing. Activation of these receptors influences descending serotonergic inhibitory pathways and may modulate nociceptive transmission within spinal and cortical circuits [11]. Psychedelics may therefore alter pain gating mechanisms, contributing to acute analgesic effects [12].

Serotonin also exerts vascular actions, functioning as both vasoconstrictor and vasodilator depending on receptor subtype engagement. Binding at serotonergic receptors located on vascular smooth muscle may influence cranial blood vessel tone, providing a potential link to historical vascular theories of CH pathophysiology [22]. Such effects may partially explain similarities between psychedelic compounds and established headache therapies sharing serotonergic pharmacology [14].

Beyond acute receptor-mediated effects, psilocybin appears capable of inducing neuroplastic changes. Experimental evidence suggests increased dendritic spine growth, synaptic remodeling, and alterations in cortical signaling that may “reset” maladaptive neural circuits involved in chronic pain states [11,12]. These findings align with contemporary organic models of CH emphasizing hypothalamic dysfunction rather than purely vascular mechanisms. The hypothalamus plays a central role in circadian regulation and autonomic control, both characteristic features of CH attacks [5]. Importantly, clinical imaging data demonstrated that changes in hypothalamic–diencephalic functional connectivity correlated with reductions in attack frequency following psilocybin administration, supporting a mechanistic link between psychedelic effects and hypothalamic network modulation [15].

Taken together, psilocybin’s combined vascular, serotonergic, and neuroplastic actions may theoretically integrate both classical vascular hypotheses and modern neurobiological models of CH involving hypothalamic circadian dysregulation.

4.3. Safety considerations

Theoretical safety profiles described in the broader literature portray psilocybin as having relatively low physiological toxicity and minimal risk of organ damage or neurotoxicity. Classic psychedelics generally demonstrate low addictive liability and do not produce physiological dependence or withdrawal syndromes [10,11]. When administered under controlled and supervised conditions with appropriate screening, adverse events are reported as uncommon and typically transient [12]. Psilocybin is frequently considered to possess one of the most favorable safety profiles among psychedelic substances [10].

Nevertheless, psychological adverse effects such as anxiety, panic reactions, or so-called “bad trips” may occur, particularly in uncontrolled environments or vulnerable individuals [10]. Rare cases of persistent psychosis have been described, emphasizing the importance of careful patient selection and supervision [11]. Long-term safety remains uncertain, especially with repeated or frequent dosing strategies such as microdosing, for which controlled data are lacking. Historical experience with methysergide—a serotonergic agent once effective in headache prevention but withdrawn due to fibrotic complications—illustrates that long-term serotonergic modulation may carry unforeseen risks [3].

Findings from clinical and observational CH studies largely align with this theoretical safety profile. In the randomized trial by Schindler et al., adverse effects such as nausea, anxiety, and fatigue were generally mild and self-limiting, with no lasting physical or neuropsychological

complications reported at follow-up [14]. Similarly, the open-label study by Madsen et al. described treatment as well tolerated [15]. Observational analyses reported no severe adverse events, although transient anxiety, discomfort, or temporary symptom worsening were occasionally described [21]. Survey studies likewise indicated manageable side effects and high patient willingness to repeat treatment despite occasional psychological reactions [17,19].

5. Conclusions

Cluster headache remains a rare yet profoundly disabling neurological disorder associated with extreme suffering, substantial psychosocial burden, and persistent therapeutic insufficiency. The relatively low prevalence of the disease contributes to a limited volume of clinical research, leaving this patient population comparatively underserved and, in many respects, neglected within contemporary headache medicine.

The severity and unpredictability of attacks exert a pervasive impact on nearly all domains of life, extending beyond pain itself to psychological distress, impaired functioning, and disrupted interpersonal relationships. For competitive athletes, these consequences may further extend to compromised training schedules, reduced performance capacity and difficulties sustaining athletic careers. Reports describing desperation illustrate that the burden of cluster headache may drive individuals to resort to self-treatment with illicit substances, including psilocybin, often without medical supervision and sometimes despite legal risks or uncertain dosing conditions. This phenomenon reflects not recreational motivation but rather an attempt to regain control over a devastating condition. However, such practices may expose patients to additional dangers, including potential substance misuse, legal consequences, and deterioration of the physician–patient relationship when disclosure of illicit drug use leads to discontinuation of medical care or loss of professional support.

At present, clinical evidence evaluating psilocybin in cluster headache remains limited in scale, and definitive conclusions regarding efficacy cannot yet be drawn. Nevertheless, the convergence of findings across available clinical and observational studies suggests a signal of therapeutic potential, particularly in preventive treatment, which warrants serious scientific attention. Importantly, reported safety outcomes across existing studies appear generally favorable, with adverse effects typically transient and manageable, supporting the feasibility of further controlled investigation under supervised conditions. While uncertainties remain regarding optimal dosing strategies and long-term outcomes, current observations indicate that

the overall risk profile may be relatively low when compared with the profound burden imposed by untreated disease.

The preliminary evidence reviewed here suggests that psilocybin may hold meaningful therapeutic potential, while simultaneously underscoring the ethical and clinical responsibility to investigate this approach systematically. The consistency of patient-reported benefits, combined with emerging mechanistic and clinical signals, provides a compelling rationale for expanding rigorous clinical research rather than dismissing these findings as anecdotal or purely expectation-driven. The potential therapeutic benefits of psilocybin could also prove valuable for athletes by reducing disease burden. We therefore join the growing body of authors emphasizing the urgent need for well-designed randomized trials, standardized dosing protocols, and medically supervised treatment frameworks to clarify both efficacy and safety [2,3,6,10,11,12,13,14,15,16,17,19,20,21]. Advancing high-quality research in this field is essential not only to determine the true role of psilocybin in cluster headache management but also to address the unmet needs of a vulnerable and often overlooked patient population.

Disclosure

Author's Contribution:

Conceptualization: ML,JC,ZC,KDW,DP,AC,MW

Methodology: ML,NT,JC,KDW,KD

Formal analysis: ML,ZC,DP,KD,AC,BC,MW

Investigation: ML,NT,JC,DP,KD,BC

Supervision: ML,JC,ZC,KDW,DP

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References

[1] Lund NLT, Petersen AS, Fronczek R, Tfelt-Hansen J, Belin AC, Meisingset T, Tronvik E, Steinberg A, Gaul C, Jensen RH. Current treatment options for cluster headache: limitations and the unmet need for better and specific treatments-a consensus article. J Headache Pain. 2023 Sep 4;24(1):121. https://doi.org/10.1186/s10194-023-01660-8

[2] Diener HC, May A. Drug Treatment of Cluster Headache. Drugs. 2022 Jan;82(1):33-42. https://doi.org/10.1007/s40265-021-01658-z

[3] Schindler EAD. Psychedelics in the Treatment of Headache and Chronic Pain Disorders. Curr Top Behav Neurosci. 2022;56:261-285. https://doi.org/10.1007/7854_2022_365

[4] Aurora SK. Etiology and pathogenesis of cluster headache. Curr Pain Headache Rep. 2002 Feb;6(1):71-5. https://doi.org/10.1007/s11916-002-0027-4

[5] Raskin NH. Serotonin receptors and headache. N Engl J Med. 1991 Aug 1;325(5):353-4. https://doi.org/10.1056/NEJM199108013250509

[6] Garfinkel, D. Headache in Athletes, The Physician and Sportsmedicine 1983 Jan;11:1, 67-76. https://doi.org/10.1080/00913847.1983.11708435

[7] Guidry, A. Crutchfield, K. Athletes with neurologic disease. Handbook of Clinical Neurology, Vol. 158 (3rd series) Sports Neurology. 2018;158:445-462. https://doi.org/10.1016/B978-0-444-63954-7.00041-0

[8] Thal, K. Mayes, C. Headache in the Athlete. Neurol Clin. 2026 Aug;44 (3): 365-379 . https://doi.org/10.1016/j.ncl.2026.03.003

[9] Burns, KN. Langford, TD. Tierney, R. McDevitt, J. Premorbid Primary Headache and Vestibular and Oculomotor Baseline Assessments in Collegiate Athletes. Clin J Sport Med. 2022 Sep 1;32(5). https://doi.org/10.1097/jsm.0000000000001002

[10] Lowe, H. Toyang, N. Steele, B. Valentine, H. Grant, J. Ali, A. Ngwa, W. Gordon, L. The Therapeutic Potential of Psilocybin. Molecules 2021, 26, 2948. https://doi.org/10.3390/molecules26102948

[11] Strand NH, Whitney M, Johnson B, Dunn T, Attanti S, Maloney J, Misra L, Gomez D, Viswanath O, Emami E, Leathem J. Pain and Perception: Exploring Psychedelics as Novel Therapeutic Agents in Chronic Pain Management. Curr Pain Headache Rep. 2025 Jan 7;29(1):15. https://doi.org/10.1007/s11916-024-01353-0

[12] Dworkin RH, Anderson BT, Andrews N, Edwards RR, Grob CS, Ross S, Satterthwaite TD, Strain EC. If the Doors of Perception Were Cleansed, Would Chronic Pain be Relieved? Evaluating the Benefits and Risks of Psychedelics. J Pain. 2022 Oct;23(10):1666-1679. https://doi.org/10.1016/j.jpain.2022.05.003

[13] Schindler EAD. The Potential of Psychedelics for the Treatment of Episodic Migraine. Curr Pain Headache Rep. 2023 Sep;27(9):489-495. https://doi.org/10.1007/s11916-023-01145-y

[14] Schindler EAD, Sewell RA, Gottschalk CH, et al. Exploratory investigation of a patient-informed low-dose psilocybin pulse regimen in the suppression of cluster headache: Results from a randomized, double-blind, placebo-controlled trial. Headache. 2022;00: 1-12. https://doi.org/10.1111/head.14420

[15] Madsen MK, Petersen AS, Stenbaek DS, Sørensen IM, Schiønning H, Fjeld T, Nykjaer CH, Larsen SMU, Grzywacz M, Mathiesen T, Klausen IL, Overgaard-Hansen O, Brendstrup-Brix K, Linnet K, Johansen SS, Fisher PM, Jensen RH, Knudsen GM. CCH attack frequency reduction after psilocybin correlates with hypothalamic functional connectivity. Headache. 2024 Jan;64(1):55-67. https://doi.org/10.1111/head.14656

[16] Sewell RA, Halpern JH, Pope HG Jr. Response of cluster headache to psilocybin and LSD. Neurology. 2006 Jun 27;66(12):1920-2. https://doi.org/10.1212/01.wnl.0000219761.05466.43

[17] Emmanuelle A. D. Schindler M.D., Ph.D., Christopher H. Gottschalk M.D., Marsha J. Weil, Robert E. Shapiro M.D., Douglas A. Wright D.C. & Richard Andrew Sewell M.D. (2015): Indoleamine Hallucinogens in Cluster Headache: Results of the Clusterbusters

Medication Use Survey, Journal of Psychoactive Drugs, https://doi.org/10.1080/02791072.2015.1107664

[18] Smedfors, G.; Jennysdotter Olofsgård, F.; Steinberg, A.; Waldenlind, E.; Ran, C.; Belin, A.C. Use of Prescribed and Non-Prescribed Treatments for Cluster Headache in a Swedish Cohort. Brain Sci. 2024, 14, 348. https://doi.org/10.3390/brainsci14040348

[19] Di Lorenzo C, Coppola G, Di Lorenzo G, Bracaglia M, Rossi P, Pierelli F. The use of illicit drugs as self-medication in the treatment of cluster headache: Results from an Italian online survey. Cephalalgia. 2016 Feb;36(2):194-8. https://doi.org/10.1177/0333102415583145

[20] de Coo IF, Naber WC, Wilbrink LA, Haan J, Ferrari MD, Fronczek R. Increased use of illicit drugs in a Dutch cluster headache population. Cephalalgia. 2019 Apr;39(5):626-634. https://doi.org/10.1177/0333102418804160

[21] Andersson M, Persson M, Kjellgren A. Psychoactive substances as a last resort-a qualitative study of self-treatment of migraine and cluster headaches. Harm Reduct J. 2017 Sep 5;14(1):60. https://doi.org/10.1186/s12954-017-0186-6

[22] Soslau G. Cardiovascular serotonergic system: Evolution, receptors, transporter, and function. J Exp Zool A Ecol Integr Physiol. 2022 Feb;337(2):115-127. https://doi.org/10.1002/jez.2554

[23] Bjurenfalk Z, Cosmo A, Simonsson O, Ran C. Lifetime classic psychedelic use and headaches: A cross-sectional study. J Psychopharmacol. 2025 Sep;39(9):968-975. https://doi.org/10.1177/02698811251324372

[24] Johnson MW, Sewell RA, Griffiths RR. Psilocybin dose-dependently causes delayed, transient headaches in healthy volunteers. Drug Alcohol Depend. 2012 Jun 1;123(1-3):132-40. https://doi.org/10.1016/j.drugalcdep.2011.10.029

[25] Rusanen SS, De S, Schindler EAD, Artto VA, Storvik M. Self-Reported Efficacy of Treatments in Cluster Headache: a Systematic Review of Survey Studies. Curr Pain Headache Rep. 2022 Aug;26(8):623-637. https://doi.org/10.1007/s11916-022-01063-5