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POLICY PAPER

LEGALISING ACCESS TO PSILOCYBIN TO END THE AGONY OF CLUSTER HEADACHES*

*SUICIDE HEADACHES/HORTON'S NEURALGIA

An ethical and evidence-based approach to treating one of the most excruciating conditions known to medicine.

NOVEMBER 2020

Legalising Access to Psilocybin to End the Agony of Cluster Headaches

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CONTENTS

EXECUTIVE SUMMARY

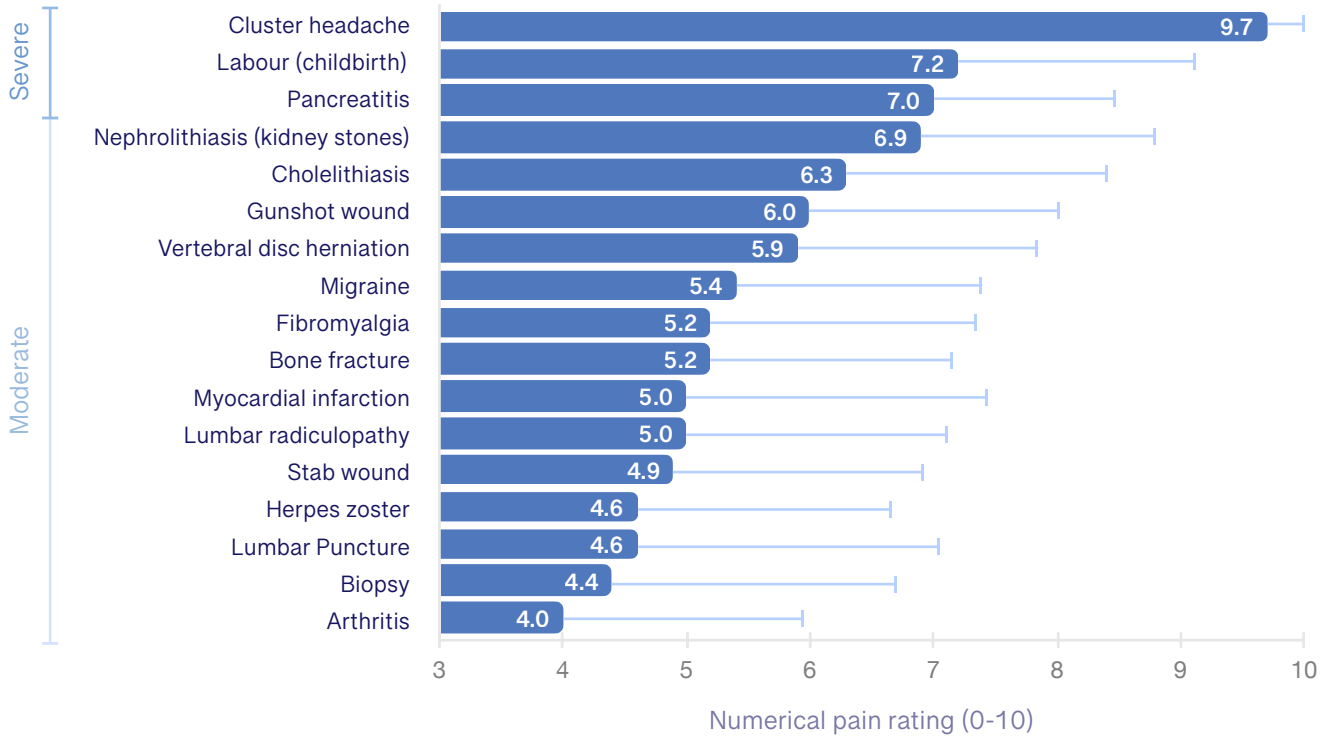
Approximately 8 million people worldwide are afflicted with possibly the most excruciating condition known to medicine: cluster headaches. Patients endure immense suffering, and many commit suicide to escape the pain. Current medical options are inadequate. Fortunately there is now clear evidence that psilocybin and chemically related substances are effective for many patients in preventing and aborting attacks. However, their legal status in most countries makes it difficult for patients to access them. Governments can dramatically improve the quality of life for many of their citizens, with little or no additional cost or risk, by removing the legal barriers to cluster headache patients accessing psilocybin and related compounds for therapeutic purposes.

CLUSTER HEADACHES: A PUBLIC HEALTH EMERGENCY

Cluster headaches, referred to informally as “suicide headaches” and also known by the older medical name Horton’s neuralgia, have been recognised as one of the most excruciating pains known to medicine.[1,2] Attacks affect one side of the head, centred on the eye, and the agony they cause is often compared to having a red-hot poker or ice pick driven through the eye into the brain. The level of pain experienced by patients is often evaluated at 10 on a scale of 0-10 – significantly higher than childbirth, kidney stones, migraines or other extremely painful conditions, especially when compared by patients who have experienced these other conditions as well (see Figure 1)[3]. It is difficult to comprehend just how agonising cluster headaches are without reading patient reports and actually witnessing an attack, such as in these videos (**link 1**, **link 2**, **link 3**).

Figure 1: Cluster headache compared to other painful conditions

Average pain ratings by cluster headache patients, with standard deviation (adapted from MJ Burish et al., 2019)



[1] Cluster Headaches and Effective Therapies. Organisation for the Prevention of Intense Suffering https://www.preventsuffering.org/cluster-headaches/

[2] Leighton J. Relieving the Pain of Cluster Headaches: video presentation https://www.youtube.com/watch?v=AbOhVahPNI0

[3] Burish MJ et al. (2019) Cluster Headache Is One of the Most Painful Human Conditions: Epidemiology of Cluster Headache and Probable Cluster Headache from a Large International Sample (poster presentation at Clusterbusters annual meeting) https://documentcloud.adobe.com/link/track?uri=urn:aaid:scds:US:30c54af9-a174-40c0-844f-03837ff611fb

Attacks typically last about one hour, with a usual range of 15 minutes to 3 hours, and they can repeat from once every second day to many times a day, sometimes as often as 8-10 times in a single day. Patients are often woken up from their sleep several times a night by attacks, and they go to extreme measures, including banging their head against the wall or punching their head, to try to distract themselves from the overwhelming pain.

About 85% of patients have episodic clusters lasting ca. 1-3 months, generally occurring seasonally once or twice a year at the same time of year, during which they have daily recurrences at the frequency mentioned. The other 15% have chronic clusters that can last for years without a break, often with several attacks every single day. Most cluster headache patients have had suicidal ideations during attacks, and many are actually driven to suicide because the pain is unbearable: suicide rates have been reported to be as much as 20x the average.[4,5]

People of both sexes and all ages can be affected, including young children. Cluster headaches are reported to affect about 1 in 1000 people and possibly as many as 3 in 1000.[6] Most countries will therefore have thousands of people within their population suffering from cluster headaches. Even though the number of people affected is relatively low compared to other diseases, cluster headaches are as common as multiple sclerosis, and the degree of suffering endured means that cluster headaches are responsible for a major fraction of all the extreme human suffering endured in many countries. Even in a small country of 5 million, a rough estimate suggests that approximately 100-200 people could be experiencing the agony of a cluster headache attack at any single moment. This makes cluster headaches a public health emergency that requires urgent attention.

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[4] Fletcher J (2015) Why Cluster Headaches Are Called “Suicide Headaches”. J Neurol Stroke 3(3): 00092. DOI: 10.15406/jnsk.2015.02.00092
https://medcraveonline.com/JNSK/why-cluster-headaches-are-called-quotsuicide-headachesquot.html

[5] Evans, Dayna. New York Magazine: Psychedelic Mushrooms Cured My Cluster Headaches. MAPS
https://maps.org/news/multimedia-library/5967-new-york-magazine-psychedelic-mushrooms-cured-my-cluster-headaches

[6] Stovner LJ, Andree C. Prevalence of headache in Europe: a review for the Eurolight project. J Headache Pain. 2010;11(4):289-299. doi:10.1007/s10194-010-0217-0
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2917556/pdf/10194_2010_Article_217.pdf

PATIENTS' DESCRIPTIONS OF THEIR PAIN

To further illustrate the level of distress, here are some actual quotes from patients in international cluster headache support groups and other sources:

"Just had a very bad Horton headache again..
I'm so scared I can't stop crying."

"Today is one of those days I wonder why I push through..."

"I don't know how to deal with this day in and day out.. wave after wave of attacks. During some of the attacks I get so desperate to make it stop that I wish I could just not exist."

"The insane pain just radiates through my brain."

"I don't know if I can live with this anymore."

"No pills work. It's the worst pain I ever had... If nothing helps I don't think I can handle this for the rest of my life."

"God, please make it stop."

"I have reached out to so many professionals and here I sit while my son screams in pain declaring his need for his life to end, I am at a loss, I have no idea what to do."

"On a scale of 1 to 10, the pain is a 50."
American football player Terrance Knighton

"I hit myself in the head to distract myself from the pain when I have a cluster headache. The pain is indescribable hell, and in desperate moments, I have hit my head against a brick wall."
Hilde Vollan, PhD candidate in bioinformatics at University of Oslo

"The pain is so shocking. There's no way anything else in life could feel worse than that. This is the feeling of death, only you don't die."
Ashley Hattle, author of Cluster Headaches: A Guide to Surviving One of the Most Painful Conditions Known to Man

STANDARD TREATMENTS: BENEFITS AND SHORTCOMINGS

There are several medical treatments that can help prevent and abort attacks.[7,8] However, no medical treatment is sufficiently effective, and many patients do not respond to treatment. Some of the most important ones include:

- Verapamil, a prescription drug used to prevent attacks. It is helpful for many patients in reducing the frequency of attacks, but it is usually only moderately effective, and for many patients it has little or no effect. It can also have cardiovascular side effects.
- Prednisone, a prescription drug used to prevent attacks. It appears to be more effective than Verapamil in reducing the frequency of attacks, but because of the serious side effects of taking oral steroids, it is usually only prescribed for about two weeks at a time, and attacks typically recur once it is stopped.
- Sumatriptan, a prescription drug that is one of the most rapid-acting and effective means to abort attacks, injected under the skin or inhaled. It doesn't always reduce the pain sufficiently, and as it can also have cardiovascular side effects, there are limits to how frequently it can be used – typically no more than twice a day. In addition, it has been observed that the more frequently a medication is taken to abort attacks, the more likely it is that "rebound" attacks will occur.
- High-flow oxygen, which can often abort an attack within minutes. This is one of the most effective and safest treatments, working for about 70-80% of patients. The effect is not immediate, typically taking 10-15 minutes to work, and so patients still endure severe pain. It does not work for all patients, and it does not prevent attacks or shorten episodes. It also requires that the patient have appropriate oxygen equipment available at all times, including when away from home.
- Electrical stimulation of the vagus nerve through a medical device can bring relief to some patients.
- Emgality, a recently approved antibody-based drug, also offers a new means to reduce the frequency of attacks in many patients, though it does not abort them.

This excerpt from an article about one patient illustrates the desperation of patients who don't obtain relief from current treatments: "Treatments vary, though Knighton said he's seen 20 to 30 doctors over the years and nothing has worked for him. Oxygen has helped some patients (not Knighton); so have injections of sumatriptan (again, not Knighton). He said sometimes these provide relief but certainly not a cure. He'll watch videos of others

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[7] Schindler, Emmanuelle and Gottschalk, Christopher. Cluster headache preventive therapies. Practical Neurology, May 2019
https://practicalneurology.com/articles/2019-may/cluster-headache-preventive-therapies

[8] Brandt RB, Doesborg PGG, Haan J, Ferrari MD, Fronczek R. Pharmacotherapy for Cluster Headache. CNS Drugs. 2020;34(2):171-184. doi:10.1007/s40263-019-00696-2
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7018790/

going through an attack, and they do the same things he does, writhing in pain, using oxygen and applying ice packs to their heads."[9]

It's worth mentioning that there are alternative, over-the-counter treatments, such as a high-dose vitamin D regimen, that seem to be helpful for some patients in preventing attacks. These treatment options deserve greater study.

EFFECTIVENESS OF PSILOCYBIN AND RELATED CHEMICALS

There is now very clear evidence that several chemicals with psychoactive properties can be remarkably effective for many patients in aborting attacks – sometimes within just a few seconds – preventing attacks, and even preventing or aborting entire cluster episodes. The evidence comes from a large number of reports from patients and systematic scientific studies based on patient surveys. The chemicals belong to the indoleamine family and include **psilocybin** (the psychoactive component of hallucinogenic mushrooms), **LSD**, **LSA** (a mild hallucinogen found in some seeds), **DMT** (the psychoactive component of ayahuasca) and **5-MeO-DALT** (a mild hallucinogen). The hallucinogenic properties of these drugs are not essential for their therapeutic effect: sub-hallucinogenic doses of psilocybin and LSD have been found to be effective in aborting and preventing cluster headaches in many patients, and a non-hallucinogenic analogue of LSD, 2-Bromo-LSD, has also been found to be effective in preventing attacks.[10] Patients sometimes use the term "busting" to refer to the use of indoleamines to abort and prevent cluster attacks and episodes.

In a 2006 study[11] on 53 cluster headache patients who had used psilocybin or LSD to treat their condition, it was found that 22 of 26 psilocybin users reported that psilocybin aborted attacks; 25 of 48 psilocybin users and 7 of 8 LSD users reported cluster period termination; and 18 of 19 psilocybin users and 4 of 5 LSD users reported remission period extension.

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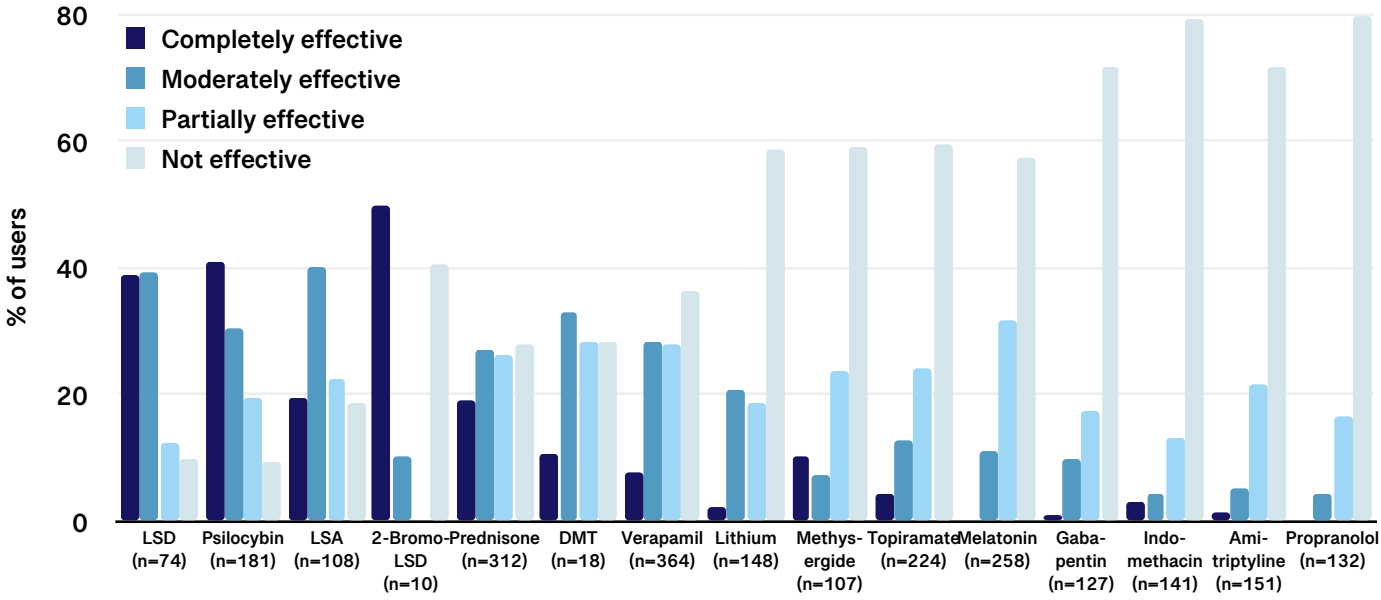
[9] Keim, John. Cluster headaches a living 'hell' for Redskins' Terrance Knighton. ESPN. 2015. https://www.espn.com/blog/nflnation/post/_/id/187390/cluster-headaches-a-living-hell-for-redskins-terrance-knighton

[10] Karst M, Halpern JH, Bernateck M, Passie T. The non-hallucinogen 2-bromo-lysergic acid diethylamide as preventative treatment for cluster headache: an open, non-randomized case series. Cephalalgia. 2010;30(9):1140-1144. doi:10.1177/0333102410363490 https://www.researchgate.net/publication/45659880_The_non-hallucinogen_2-bromo-lysergic_acid_diethylamide_as_preventative_treatment_for_cluster_headache_An_open_non-randomized_case_series

[11] Sewell RA, Halpern JH, Pope HG Jr. Response of cluster headache to psilocybin and LSD. Neurology. 2006;66(12):1920-1922. doi:10.1212/01.wnl.0000219761.05466.43 http://www.en.psilosophy.info/pdf/response_of_cluster_headache_to_psilocybin_and_lsd_(psilosophy.info).pdf

In a 2015 study[12] by Yale University medical researcher Prof. Emmanuelle Schindler and colleagues on 496 cluster headache patients, **both psilocybin and LSD were found to provide >70% of patients who tried them with at least moderate protection from attacks, and complete preventative efficacy in ca. 40% of cases – greater than that reported for any other conventional medication** (see Figure 2). Several participants reported that a single dose of psilocybin or LSD prevented attacks, shortened/aborted a cluster period, or induced remission from chronic cluster headache. The authors wrote that **"there was little mention of negative effects"** and that **"these drugs are historically safe."**

Figure 2: Effectiveness in preventing cluster headaches
(adapted from E. Schindler et al., 2015)



From the abstract: "The indoleamine hallucinogens, psilocybin, lysergic acid diethylamide [LSD], and lysergic acid amide [LSA], 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 headache into remission more so than conventional medications. Furthermore, infrequent and non-hallucinogenic doses were reported to be efficacious."

[12] Schindler EA, Gottschalk CH, Weil MJ, Shapiro RE, Wright DA, Sewell RA. Indoleamine Hallucinogens in Cluster Headache: Results of the Clusterbusters Medication Use Survey. J Psychoactive Drugs. 2015;47(5):372-381. doi:10.1080/02791072.2015.1107664
https://pubmed.ncbi.nlm.nih.gov/26595349/
https://www.tandfonline.com/doi/full/10.1080/02791072.2015.1107664

The same study also found psilocybin to be effective as an abortive, comparable to high-flow oxygen. Another more recent study by Prof. Larry Schor, based on a survey of several thousand cluster headache patients, similarly found that psilocybin was at least as effective as oxygen as an abortive.[13]

The efficacy of these substances in reducing the frequency of attacks and even preventing entire episodes makes them uniquely valuable as treatments that can spare patients huge amounts of agony, restore their ability to function and give them their lives back.

Two Phase I randomised controlled clinical trials on psilocybin for the treatment of cluster headaches are currently underway in late 2020 and are expected to provide further evidence of efficacy.[14,15] Interestingly, there are new clinical trial data providing evidence for the efficacy of psilocybin in treating migraine headaches as well.[16]

The compound 5-MeO-DALT, which is only mildly hallucinogenic, has received less attention. However, researcher Mitchell Post has compiled numerous patient testimonials of the efficacy of this compound in preventing attacks.[17,18]

According to numerous anecdotal reports, inhaled DMT can abort an attack in as little as 3-5 seconds.[19] As it is a powerful hallucinogen, it needs to be used with caution. However, it may be the most rapidly acting substance known for aborting cluster headache attacks, and anecdotal evidence suggests that lower, sub-hallucinogenic doses can also abort attacks in some patients.

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[13] Schor L, Burish M and Pearson S. Cluster Headache: Investigating Severity Of Pain, Suicidality, Personal Burden, Access To Effective Treatment, And Demographics Among A Large International Survey Sample (poster presentation at Clusterbusters annual meeting). 2018
https://documentcloud.adobe.com/link/track?uri=urn:aaid:scds:US:1bd33c71-b4db-4092-8f12-2f6b26191954

[14] Psilocybin for the Treatment of Cluster Headache. Clinical trial.
https://clinicaltrials.gov/ct2/show/NCT02981173

[15] Prophylactic Effects of Psilocybin on Chronic Cluster Headache (EPOCH). Clinical trial.
https://clinicaltrials.gov/ct2/show/NCT04280055

[16] Schindler EA et al. Preliminary Analysis of the Sustained Effects of a Single Low Oral Dose of Psilocybin in Migraine Headache. 62nd Annual Scientific Meeting American Headache Society. Headache. 2020;60:1-156. doi:10.1111/head.13854
https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.13854

[17] Post, Mitchell. Treatment of Cluster Headache Symptoms using Synthetic Tryptamine N,N-Diallyl-5 Methoxytryptamine. 2014
https://www.academia.edu/7800647/Treatment_of_Cluster_Headache_Symptoms_using_Synthetic_Tryptamine_N_N-Diallyl-5_Methoxytryptamine

[18] Post, Mitchell. Cluster Headache Patient Survey: 5-MeO-DALT. 2015
https://www.academia.edu/11884483/Cluster_Headache_Patient_Survey_5-MeO-DALT

[19] Frerichs, Quintin. Treating Cluster Headaches Using N,N-DMT and Other Tryptamines. 2019
https://qualiacomputing.com/2019/08/05/treating-cluster-headaches-using-nn-dmt-and-other-tryptamines/

PATIENT TESTIMONIALS OF EFFICACY

The following are just a few of the many testimonials from patients, including in cluster headache support groups, in which they attest to the efficacy of psilocybin mushrooms and related substances:

“My cluster headaches began in the beginning of the 1990's in my late teens. I had attacks every night and I had to stop my studying. I spent 15 years trying everything available in the form of pharmaceuticals, and I had surgical operations done. But my cluster headaches got steadily worse and eventually I turned chronic. At this point I was on 8 different medications when I was hospitalised. I couldn’t walk and could barely speak or remember things. I was waiting for brain surgery and feared for my life. When I consulted with another neurologist the doctors treating me took offence and sent me home. It was horrible. I lived as a physical, mental and emotional cripple with my parents at the age of 35 and was preparing to depart this planet. Then through the Clusterbusters organisation I found other patients and for the first time I received help and advice that were thought out and based on experience. After “detoxing” from my medications over a period of nearly 2 years, I ate mushrooms I received in the mail. My daily 6-8 severe cluster attacks had been happening for 500+ days straight. My second dose of mushrooms made my attacks stop completely.

I had not been expecting anything like this – my doctors had said that mushrooms caused death, schizophrenia or psychosis. I wanted to tell the whole world what I had found and what I kept learning, but no one in my hospital wanted to hear it. But there were already many others who had similar amazing results. I created a Finnish Facebook group in 2012 and last year we finally formed an association. It has been an exhausting 8 years but during this time I have seen hundreds of patients with cluster headaches self-medicate with psychedelics. Psychedelics save and heal lives. One might expect I would have some bad experiences to share, but I really don’t have any.”

– Tony Taipale, President, Finnish Horton Association

“When my Dad started begging me for help with anything or he was going to shoot himself, I immediately got on this site and found mushrooms. (...) I went to his home 86 miles away at 10 at night once I got them. He has not had one headache since. (...) It IS a LIFESAVER for him, microdosing. Months and months of begging and crying from a tough 79-year-old farmer. He is fine now.”

– K.B., family member

“Psilocybin mushrooms have been the only thing that has ever worked.”

– M.C., cluster headache patient

“I had migraines starting when I was 12. When I was about 20, I developed a new kind of headache. I went to several doctors and they gave me several medicines. It continued like this for 25 years. I had two children and after that I became chronic, with headaches every day and night. My headaches became worse and more pills were added to the list. Finally when I was 45 years old, a neurologist told me I suffer from cluster headaches and gave me more medicines. One year later I was in such bad condition that I really couldn't take it anymore. 12 attacks per day, I could not keep food down or regulate my temperature. Just trembling and shivering between the attacks and having a terrible headache all the time. I received oxygen along with all the medicines and it did work a little.

Then I found a Facebook group where people told me that there are mushrooms that work. I left all the medicines and I started busting. It was not easy at the beginning, as I had attacks during trips and rebound headaches. But eventually, after almost a year, I could stretch the days between busting and the attacks were just a few every now and then. Now four years later I use mushrooms when I feel it coming, and I don’t remember when I last had a cluster attack. I would not be here if I would not have found mushrooms. I had already said goodbye to my children.”

– M.K., cluster headache patient

“People don't talk about this enough. I busted last summer after my worst cycle ever, and 15 years of suffering, and I haven’t even had a twinge since.”

– N.P., cluster headache patient

“If you really want your life back, look into psychedelics. Mushrooms, LSD and DMT. With mushrooms and LSD, if taken in the correct regimen, you can bust a cycle. DMT will abort an attack in 5 seconds and back to sleep.”

– A.C., cluster headache patient

“I started with clusters at age 20. Absolutely disabling until I tried LSD when I was about 44. 2 tiny doses 6 months apart. I have been headache-free and able to maintain on meds since then. I had to go the illegal route, but I swear by it. It was a miracle. I am 54 years old now.”

– L.P., cluster headache patient

“The mushrooms did exactly what I was told they would do. The only “side effect” is realising I should have done this a long time ago. This is the first time in five years I leave my dwelling without an oxygen tank – the fear is gone, the trauma is under control.”

– A.H., cluster headache patient

“I've been battling the beast for many years, twice a day, with no relief. But on New Year’s Eve 2019/2020 a friend gave me a couple of magic mushrooms and bingo! No more headaches! As of now it seems like I got my life back without the cluster headaches occurring.”

– R.H., cluster headache patient

“I am a chronic cluster headache patient and am using psilocybin. I haven't eliminated my attacks completely; however, my attacks went from daily, averaging 1-4 per day, to 1-4 per month currently. So it's been a slower road for me, but the results are nothing short of a miracle considering where I was just 6 months ago, not even thinking where I was a year ago!”

– A.W., cluster headache patient

“I’ve been doing this for 4 years now. I used to get cycles in the spring and fall. Now the only time I get a cycle is when I can’t find mushrooms. I usually take them a month or two before a cycle is supposed to start. They have truly changed my life. Finally a cage that can contain the beast! Freedom!”

– G.K., cluster headache patient

“I am the mother of a 10-year-old boy who has had cluster headaches since he was around 3 years old. He gets a 9-day cluster twice a year, every year, within three days of the date the year before. Due to his age there aren’t very many pharmaceutical options for him to try. We have been preparing ourselves for his April cluster, which hit last year on the 19th. So last month we started microdosing magic mushrooms.... and so far no cluster headache!! We are over the moon about this!!! This is the first time he has had a break in about 5 years!”

– A.N., mother of cluster headache patient

“For me, growing up in the 60's-70's, the propaganda machine worked, and although I knew people were using psychedelics to treat their cluster headaches, I was way too fearful to try any alternative options. When a new cycle started in 2008, I stuck with traditional medicine and increased the dosages, but I continued to scream nightly, feeling as though I was in a knife fight. I finally decided to try psychedelics. Sub-hallucinogenic doses of psilocybin tea gave me some substantial runs of pain-free time, but the clusters always returned. In 2014, I heard about 5-MeO DALT and bought some online. I measured out 16 mg using a jewellery scale, put it in a gel cap and took it. That was it. Not another cluster headache. This month I will celebrate 6 years of being pain-free.”

– C.R., cluster headache patient

“I am a chronic sufferer. Mushrooms have made my life liveable again. I microdose as an abortive.”

– H.M., cluster headache patient

“My condition is described as VERY SEVERE and when these attacks began, I needed to talk to my neighbours and explain why I would be screaming every night from 11 pm until more or less, if I was lucky, 5 am, where already after so many repetitions of that incessant and sharp stabbing pain, I would faint, either from pain, exhaustion or from overdose of medications that are useless. (...) I had already tried all the medications, all the therapies, all the doctors, acupuncture, cables in my head... I had been with the attacks inside a tomography machine. And nothing worked... I had tried with chiropractors, therapeutic massages, relaxing, improving my diet, cutting this or that, stopping going to work, tryptamines, one bottle of tramadol a day for months, anticholinergic treatments (...) Researching on the internet, I learned about psilocybin. In September 2017 it cured me, and since then... I am no longer afraid of going to sleep.”

– D.F., cluster headache patient

PATIENTS' EXPERIENCES REPRESENT POWERFUL, ESSENTIAL EVIDENCE

For new medicines to be approved for commercialisation, randomised controlled trials (RCTs) are required to demonstrate safety and efficacy. This standard procedure helps to protect patients from experiencing dangerous side effects, provides information on the efficacy of new substances compared to existing ones, and also helps ensure that new medications are effective enough to justify the often high price commanded by pharmaceutical companies.

However, RCTs are not always possible, due for example to small patient numbers and lack of funding. The latter is especially relevant to substances that are not patentable and therefore of minor interest to pharmaceutical companies. When the substances are tightly controlled due to drug laws, it is more difficult to organise such trials. Furthermore, when there is already strong evidence of high efficacy, there are ethical questions about depriving patients of a medicine in the control arm of a trial.

> "The efficacy of these substances in reducing the frequency of attacks and even preventing entire episodes makes them uniquely valuable as treatments that can spare patients huge amounts of agony, restore their ability to function and give them their lives back."

A large number of patient reports can provide a strong body of evidence for the effectiveness of a compound even in the absence of a large clinical trial. This is the case for cluster headaches, where likely thousands of patients have achieved relief from unbearable pain and recovered their lives using psilocybin-containing mushrooms and other related chemicals. Many patients with chronic cluster headaches that persisted for years, or cluster headache episodes that lasted for months and repeated every year, found that the attacks quickly stopped after the ingestion of a few doses of psilocybin. These reports provide powerful evidence of efficacy in preventing attacks. While surveys and patient reports are subject to recall bias and other limitations, it is vanishingly improbable that the dramatic effect observed independently by so many patients was due to chance or artefact. There is statistical near-certainty about the effectiveness of these indoleamines in treating a substantial fraction of patients.

The chemical similarity of these different substances points to a common mechanism of action underlying this efficacy. An unrelated substance such as cannabis has generally been found to be unhelpful or even to worsen attacks.

Furthermore, in a recent review from January 2020 titled "Pharmacotherapy for Cluster Headache"[8], the authors wrote: "As cluster headache has a high disease burden, medication with a low level of evidence must be tried in daily practice." In other words, because cluster headaches are so excruciatingly painful, we must allow patients to try promising therapeutics even without the results of large-scale RCTs.

SAFETY OF PSILOCYBIN AND OTHER INDOLEAMINES

Aside from their efficacy, psilocybin and related substances are probably safer to use than many standard cluster headache treatments. A 2010 study of the harm caused by different drugs used recreationally found that psilocybin mushrooms and LSD had scores of 6 and 7, respectively, on a scale of 0-100 (where 100 is the highest level of harm), while alcohol, at the other end of the scale, had a score of 72.[20] A recent Phase I clinical trial on psilocybin in healthy volunteers found no serious adverse effects.[21] Additionally, when used in a preventative capacity, these substances have often been found to prevent cluster headache episodes after just a few doses, limiting their capacity to cause harm compared to medications with significant side effects that need to be used daily.

A 2018 scientific review paper on psilocybin[22] reported that:

- Psilocybin mushrooms have been used for millennia for spiritual and medical purposes.
- Animal and human studies indicate low abuse and no physical dependence potential.
- Major national surveys indicate low rates of abuse, treatment-seeking and harm.

The authors wrote: "It is the opinion of the authors of this review that the original placement of psilocybin [in Schedule I] was the result of a substantial overestimation of the risk of harm and abuse potential."

The 2020 report "Medicinal Use of Psilocybin" by the Conservative Drug Policy Reform Group (CDPRG), a UK-based organisation that advocates for evidence-based drug policy, states: "Psilocybin…is associated with a low potential for harm relative to other classes of

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[20] David J. Nutt et al, Drug harms in the UK: A multi-criterion decision analysis, Lancet 2010, 376: 1558–65 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)61462-6/fulltext

[21] COMPASS Pathways and King's College London Announce Results From Psilocybin Study In Healthy Volunteers. 2019. Press release. https://www.prnewswire.com/news-releases/compass-pathways-and-kings-college-london-announce-results-from-psilocybin-study-in-healthy-volunteers-300973347.html

[22] Johnson MW, Griffiths RR, Hendricks PS, Henningfield JE. The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. Neuropharmacology. 2018;142:143-166. doi:10.1016/j.neuropharm.2018.05.012 https://www.sciencedirect.com/science/article/pii/S0028390818302296?via%3Dihub

psychoactive drugs: it has very low toxicity, its use is not associated with the development of physical dependence, nor with acquisitive or other crime, and deaths attributed to its abuse are extraordinarily rare. (…) There is overwhelming scientific consensus that the current legal status of psilocybin is not evidence-based, but rather grounded in overstated historical assumptions of harm."[23]

COST

Because they do not need to be used as frequently and are inexpensive to produce, the alternative treatments mentioned offer the potential to dramatically reduce the cost of treatment compared to current medical options. Although cost is of secondary importance compared to efficacy, it represents a further argument for reduced burden to society.

LEGAL STATUS

Although psilocybin mushrooms are not regulated by UN treaties, they are currently illegal to possess or cultivate in most countries, with some countries putting them in the same category as far more dangerous drugs.[24] Notable exceptions include Brazil and Jamaica, as well as the Netherlands, where they can be purchased in the form of truffles. Access is facilitated in some other jurisdictions. In Canada, grow kits are legal, and the online sale of psilocybin appears to be tolerated. In the US, grow kits are legal in most states, and a few cities such as Denver and Oakland have decriminalised possession of psilocybin. The citizens of the state of Oregon voted in late 2020 to legalise access to psilocybin therapy for depression and anxiety, indications where there is now strong evidence for psilocybin having therapeutic potential as well.[25] In August 2020, the Canadian government gave explicit approval to four terminal cancer patients to use psilocybin for end-of-life therapy.[26]

Portugal has decriminalised all drugs, and in Austria, Italy, Spain and the Czech Republic, possession and culture of psilocybin mushrooms have been decriminalised, with cultivation legal in Austria if not intended to be used for consumption. Other countries have also decriminalised cultivation or possession, or do not enforce prohibition.

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[23] Rucker J et al. Medicinal Use of Psilocybin: Reducing restrictions on research and treatment. 2020. https://www.cdprg.co.uk/s/8-FULL-REPORT-Medicial-Use-of-Psilocybin.pdf

[24] Smith, Patrick. What Is The Legality Of Psilocybin Mushrooms? The Third Wave. 2 March 2017 https://thethirdwave.co/legality-psilocybin-mushrooms/

[25] Psilocybin for Depression Study. Beckley Foundation https://www.beckleyfoundation.org/psilocybin-for-depression-2/

[26] Lindsay, Bethany. 4 Canadians with terminal cancer win the right to try magic mushrooms. CBC News. 5 August 2020 https://www.cbc.ca/news/canada/british-columbia/magic-mushrooms-therapy-1.5675637

LSD and DMT are both Schedule I drugs under the UN Convention on Psychotropic Substances and are illegal in all but a handful of jurisdictions, with often severe penalties for possession. Plants containing DMT are not as tightly regulated.

It is certain that measures will continue to be taken in a greater number of jurisdictions to allow the use of psilocybin and other substances for both medical and recreational purposes, in keeping with the trend towards evidence-based drug policies focused on harm reduction, that favour decriminalisation and legalisation of controlled substances, including cannabis.

CONSEQUENCES OF CURRENT DRUG POLICIES FOR CLUSTER HEADACHE PATIENTS

The legal status of psilocybin in most jurisdictions, as well as the other substances mentioned, make them difficult to obtain for cluster headache patients desperately seeking to relieve their pain, unless they have reliable sources or a supportive patient community located nearby. Although growing their own mushrooms is a solution opted for by many patients in some countries as a means of ensuring a reliable supply, it is an unnecessary burden for people in extreme pain to have to become competent fungiculturists in order to produce a medicine that works.

Patients also risk a criminal record if they attempt to purchase these substances, or even kits to grow their own mushrooms, depending on the jurisdiction. They are therefore deterred from seeking pain relief by the fear of breaking the law and by the social stigma of using illegal substances. As Finnish researcher Tuukka Tammi has said about the situation in his own country: “While sanctions for minor drug offences are not very heavy (usually a fine or a warning), simply being caught using drugs can have profoundly negative effects on a person’s life – even if they are not criminally prosecuted. Someone found using drugs will have their name entered into a police database – where it can be stored for up to ten years, with the possibility of the offence being discovered by future employers in the case of a background check.”[27]

Patients also have difficulty to obtain reliable information from reputable sources on how to acquire and use these therapies. Even cluster headache associations and patients may be reluctant to talk about or share information about how useful these substances are, for fear of repercussions for their reputation. This de facto culture of silence and the social stigma

[27] Sárosi, Péter. “Finland Needs to Relax Its Restrictive Drug Laws – An Interview with Tuukka Tammi”, Drug Reporter, 25 February 2019
https://drogriporter.hu/en/tuukka/

encouraged by strict drug laws mean that valuable information is kept hidden from those who need it.

> "It is entirely reasonable for a patient in excruciating pain to seek out any treatment that works. When standard medical options are unsatisfactory, it is entirely reasonable for the patient to seek alternatives. Criminalising reasonable behaviour is unreasonable: it victimises people unlucky enough to suffer a terrible condition, who harm no one by seeking relief of their pain."

The legal status also means that many doctors discourage the use of these substances by patients and instead insist on conventional therapies that often do not work. Even among doctors who are aware of their therapeutic efficacy, in most jurisdictions they are not authorised to simply prescribe these substances, even for compassionate use. Although doctors should ideally be trusted to provide the best available knowledge on how to treat a condition, they are often less informed or able to help cluster headache patients than fellow patients are.

ETHICAL CONSIDERATIONS

It is an imperative to alleviate suffering, and especially extreme suffering, according to any mainstream ethical framework.[28] This means that people in extreme pain must be able to access effective treatments. When governments restrict such access instead of ensuring it, compel patients to break the law or impede the development of such treatments out of excessive caution, their policies are not aligned with their ethical responsibilities. Of course, care must be taken to ensure that the medicine is not worse than the disease, and that a drug does not actually cause more harm than it relieves. However, in the case of cluster headaches, the benefits in terms of alleviated suffering are so much greater than any risk of additional harm being caused, and few additional resources are needed to achieve these benefits. The restrictions currently in place allow extreme suffering to persist that could easily be prevented.

It is entirely reasonable for a patient in excruciating pain to seek out any treatment that works. When standard medical options are unsatisfactory, it is entirely reasonable for the patient to seek alternatives. Criminalising reasonable behaviour is unreasonable: it

[28] Vinding, Magnus. Suffering-Focused Ethics: Defense and Implications. Copenhagen: Ratio Ethica, 2020 https://magnusvinding.com/2020/05/31/suffering-focused-ethics-defense-and-implications/

victimises people unlucky enough to suffer a terrible condition, who harm no one by seeking relief of their pain.

A society that values transparency, authenticity and compassion needs to destigmatise discussions about effective approaches to relieving suffering. As journalist Jani Kaaro has written: “If a psychedelic could significantly contribute to the treatment of a disease, but one cannot get it from a doctor, what does that mean for the patient’s human rights?” “[Jarkko, a cluster headache patient] says he carries a double burden, the first being the disease itself and the second the constant fear of being caught and its legal consequences.” “Can’t society find some compromise where he could get effective treatment for his illness without having to live as a criminal?”[29]

HUMAN RIGHTS PERSPECTIVE

Among the rights[30] guaranteed to all human beings under international treaties are:

- The right to the highest attainable standard of health
- Freedom from torture and cruel, inhuman or degrading treatment or punishment

Freedom from preventable pain is a cornerstone of these fundamental human rights. The UN Special Rapporteur on torture and other cruel, inhuman or degrading treatment or punishment, Juan E. Méndez, wrote in a 2013 report: “When the failure of states to take positive steps, or to refrain from interfering with health-care services, condemns patients to unnecessary suffering from pain, states not only fall foul of the right to health but may also violate an affirmative obligation under the prohibition of torture and ill-treatment.”[31]

While psilocybin itself is not currently on the WHO Essential Medicines list, and while no one would suggest that there is any wilful intent in most progressive countries to deprive patients of effective pain medication, the above statement illustrates the seriousness of the issue and the obligation of states to take reasonable measures to remove obstacles to pain relief – and all the more so when it actually concerns torture-level suffering.

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[29] Kaaro, Jani. Säkenöivästä Voimasta: Kuinka Psykedeelejä Voisi Käyttää Lääkkeinä? (About Sparkling Power: How Could Psychedelics Be Used As Medications?) Rapport. 2 November 2016
https://www.rapport.fi/journalistit/jani-kaaro/sakenoivasta-voimasta-kuinka-psykedeeleja-voisi-kayttaa-laakkeina

[30] Frequently Asked Questions On A Human Rights-based Approach To Development Cooperation. United Nations. 2006
http://www.ohchr.org/Documents/Publications/FAQen.pdf

[31] Report of the Special Rapporteur on torture and other cruel, inhuman or degrading treatment or punishment, Juan E. Méndez. United Nations General Assembly. A/HRC/22/53. 1 February 2013
http://www.ohchr.org/Documents/HRBodies/HRCouncil/RegularSession/Session22/A.HRC.22.53_English.pdf

POLICY OPTIONS AND RECOMMENDATIONS

Policy-making must be based on an ethic of compassion and the rational use of evidence towards harm reduction. Our strong overall recommendation is therefore to remove the legal and practical obstacles to cluster headache patients acquiring treatments such as psilocybin for personal use. There are a few possible policy options available that are not mutually exclusive:

1 Allow medical prescription of psilocybin and related indoleamines

Existing regulations must be modified to allow doctors to prescribe currently restricted indoleamines such as psilocybin, LSD, DMT and 5-MeO-DALT to patients with cluster headaches, and to ensure that these substances can be readily produced or imported for such medical use. These measures would have a range of hugely important benefits. They would ensure that patients can reliably obtain these substances at a known dosage and purity, without the practical and legal uncertainties they currently face. They would also lead to these substances becoming recognised as valid treatments, promote the sharing of information within the medical and patient communities, and facilitate the acquisition of new data on optimal use.

2 Decriminalise/legalise use of psilocybin and related indoleamines by cluster headache patients

Although the ideal solution is for these substances to become readily available through the medical system, we also recommend that existing regulations be modified to ensure that patients with a cluster headache diagnosis who purchase or possess small amounts of psychoactive substances, or who purchase and use grow kits for psilocybin-containing mushrooms, for personal therapeutic use, cannot be legally prevented from doing so or be charged with a crime or offence. This measure would be especially important as long as there are any practical or legal barriers to medical access to any of these substances, taking into account that patients may respond better to some substances than to others. It would also remove an ethical incongruity in current legislation in which patients can be criminalised for trying to relieve their pain.

3 General decriminalisation/legalisation

This policy paper has not set out the case for a more general shift in drug policy. We mention it here as an available policy option because it would also reduce many of the legal and practical barriers to self-treatment by cluster headache patients. An approach to drug policy focused on harm reduction would involve the

decriminalisation and/or legalisation of the acquisition and possession for personal use of all psychoactive substances, and the legal regulation of the manufacture, sale and transport of low-risk psychoactive substances, including psilocybin and LSD.

There are strong reasons for adopting this approach, based on public health and other considerations, as argued elsewhere by many international organisations, including the Global Commission on Drug Policy[32], the International Drug Policy Consortium[33] and others.[34]

An example of a statement that could be issued by a government to explain new policies and regulations aimed at providing relief to cluster headache patients within a larger ethical context:

"Cluster headaches are an extremely painful condition that affects thousands of people in our country, leading some to commit suicide. Many obtain dramatic relief with substances that have psychoactive properties. Although further studies are ongoing, there is already solid evidence that these substances are safe and effective, in some cases more so than existing medications. It was never the intention of our drug laws to create more suffering, or to punish those seeking relief from pain. We propose to allow medical doctors to legally prescribe such substances for the treatment of cluster headaches. We also propose to modify existing legislation so that no one purchasing or using psychoactive substances for relief from cluster headaches can be charged with a crime.

These measures are in keeping with our goal of a more compassionate society that seeks to reduce harm and suffering, using rational, evidence-based decision-making. We will continue to modify existing policies when it is warranted by the evidence."

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[32] Advancing Drug Policy Reform: A New Approach To Decriminalization. Global Commission on Drug Policy. 2016 Report
https://www.globalcommissionondrugs.org/wp-content/uploads/2016/11/GCDP-Report-2016-ENGLISH.pdf

[33] Drug Law Reform. International Drug Policy Consortium
https://idpc.net/policy-advocacy/drug-policy-reform

[34] Rorheim, A. and Roll Spinnangr, I. Effective Drug Policy: An Evidence-based Approach. Effective Altruism Foundation policy paper. 2016
https://ea-foundation.org/files/effective-drug-policy.pdf

POSSIBLE CONCERNS AND RESPONSES

Is it not necessary to wait for definitive clinical trial results before allowing patients to acquire these substances legally?

There are different levels of evidence. Randomised controlled trials showing safety and efficacy are usually necessary for drug approval. However, other forms of evidence may be sufficient to make informed policy decisions, especially when safety information exists and there is good reason to believe that the benefits far outweigh any risks. The urgency represented by cluster headaches means that waiting many years for new clinical trials or for drugs to be developed will allow extreme suffering to occur that could be relieved.

Shouldn't countries depend as well on the recommendations of the pharmaceutical industry in deciding which substances to allow?

There is ample evidence that pharmaceutical companies will often put profits above the interests of patients, which may include the use of alternative or low-cost therapies. The interest of patients must always come first, and policies must be based on objective evidence of effectiveness.

Does a change in policy send a signal that taking drugs is "ok"?

It sends a signal that overly strict drug policies can do more harm than good, that policies should be based on their actual impact in reducing suffering, and that black-and-white policies do not reflect reality. There is mounting evidence for medical benefits of psychoactive substances. A growing number of clinical trials on psilocybin, LSD and MDMA for the relief of post-traumatic stress disorder (PTSD) and depression, and the global trend towards decriminalisation/legalisation of marijuana, are de-stigmatising the use of psychoactive substances. The wider issue of whether drugs should be decriminalised/legalised is a discussion that needs to be had, informed by evidence from other countries that have taken this approach, with a focus on overall harm reduction, human rights and other considerations. The legality of using drugs to alleviate pain and treat other conditions is entirely consistent with approaches aimed at minimising recreational drug use among adolescents.

Why should any country take the lead on this issue?

COVID-19 has added a new element of instability to our world, and people are looking for better governance and leadership that is compassionate, evidence-based and responsive to needs, including those of the least well off or the most vulnerable. The ability of a government to respond to new information and implement low-risk policies that can relieve the extreme suffering of cluster headache patients is a good indicator of its resolve to provide the kind of leadership our world needs in tackling the many other issues we face that cause intense suffering.

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The Organisation for the Prevention of Intense Suffering (OPIS) is a think-and-do tank designing and promoting blueprints for a compassionate society grounded in deep ethical thinking. Our vision is a world that eliminates the preventable suffering of all sentient beings. We advocate for solutions to specific causes of intense suffering in both human and non-human animals, and we promote compassionate, evidence-based decision-making where the prevention and alleviation of intense suffering is given the highest priority, within a system that aims to meet the needs of all. OPIS was founded in 2016 and is based in Geneva, Switzerland.

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