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Indoleamine Hallucinogens in Cluster Headache: Results of the Clusterbusters Medication Use Survey

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Abstract—Cluster headache is one of the most debilitating pain syndromes. A significant number of patients are refractory to conventional therapies. The Clusterbusters.org medication use survey sought to characterize the effects of both conventional and alternative medications used in cluster headache. Participants were recruited from cluster headache websites and headache clinics. The final analysis included responses from 496 participants. The survey was modeled after previously published surveys and was available online. Most responses were chosen from a list, though others were free-texted. Conventional abortive and preventative medications were identified and their efficacies agreed with those previously published. 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 headache into remission more so than conventional medications. Furthermore, infrequent and non-hallucinogenic doses were reported to be efficacious. Findings provide additional evidence that several indoleamine hallucinogens are rated as effective in treating cluster headache. These data reinforce the need for further investigation of the effects of these and related compounds in cluster headache under experimentally controlled settings.

Keywords—cluster headache, hallucinogens, Internet survey, lysergic acid amide, lysergic acid diethylamide, psilocybin

Cluster headache, often rated the most painful of all primary headache disorders, causes significant disability, with enormous personal, economic, and psychiatric burden (Robbins 2013; Rozen and Fishman 2012). The term "suicide headache" reflects the extraordinary intensity and relentless nature of these attacks (Horton 1952; Robbins 2013). In standard parlance, a *cluster attack* refers to the discrete paroxysm of pain—a unilateral stabbing that is primarily retro-orbital, lasting 15–180 minutes, occurring several times daily, usually at strikingly predictable times. A *cluster period* refers to the duration of time during which attacks occur regularly, ranging from weeks to years, often occurring at the same time each year. A *remission period* refers to a prolonged attack-free interval. In episodic cluster headache, periods are separated by months to years. In chronic cluster headache, the period lasts for over a year with no remission greater than one month. The etiology of cluster headache is incompletely

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understood, though several anatomical features have been identified. Functional neuroimaging and deep brain stimulation (DBS) have demonstrated that cluster attacks correlate with focal hypothalamic activity (Cohen and Goadsby 2006; Schoenen et al. 2005; Starr et al. 2007). Activation of autonomic nuclei and ganglia subtend ptosis, miosis, lacrimation, and rhinorrhea, all characteristic and diagnostic elements of an attack (May 2005). Activation of the first division of the trigeminal nerve is the primary source of facial and head pain in cluster headache (May 2005).

Oxygen inhalation at a high rate (12–15 L/min) and subcutaneous triptan administration are mainstays of acute abortive treatment in cluster headache. Verapamil, often at high doses (480–960 mg daily), corticosteroids, and other neuromodulators are used to suppress attacks, shorten the duration of cluster periods, and induce remission (May 2005). Taken on a daily basis, however, prophylactic medications are not without unwanted effects (Matharu et al. 2005). Furthermore, an estimated 10–20% of cluster headache patients are refractory to medical therapy (May 2005). Surgical intervention, such as implantable occipital nerve stimulators or hypothalamic DBS, is effective in about half to two-thirds of patients (Magis and Schoenen 2012).

Clusterbusters.org is a website founded by a so-called "clusterhead" who resolved to share the discovery that the hallucinogenic compound, lysergic acid diethylamide (LSD), treated his cluster headaches. Clusterbusters, Inc. is a non-profit organization based in Illinois dedicated to the education and research of cluster headache. LSD, psilocybin, and other alternative therapies are openly discussed on the website's public message board. Recently published cases and results from an online survey support the ability of the indoleamine hallucinogens, LSD and psilocybin, to abort attacks, induce remission, and prolong the duration of remission (Matharu et al. 2005; Sewell, Halpern, and Pope 2006). No other single drug class has been reported to have all these clinical benefits. Clusterbusters members Marsha J. Weil and Douglas A. Wright developed an Internet medication use survey in order to further characterize the effects of both traditional and alternative therapies in cluster headache.

METHODS

Subjects and Study Design

The survey was created and carried out by Clusterbusters, Inc. Subjects were recruited from cluster headache websites and headache clinics. Those registered at clusterbusters.org received two e-mails in May 2012. The survey was also advertised at clusterheadache.com, cluster headache sites on Facebook, and the numerous headache clinics listed at migraines.org. A description of the survey was provided on those websites. Participation was entirely voluntary and confidential. No information was obtained from sources other than the survey itself. Data provided for analysis contained no personal identifying or health information; thus, subjects remained anonymous to those interpreting the results. The survey was modeled after those previously published in the literature and available online (Rozen and Fishman 2012). The survey was open from May 2, 2012, until July 11, 2012, and contained 41 questions that included demographics, headache characteristics, smoking and drinking habits, and medications. Medication effectiveness was assessed by a four-tier rating scale that included not effective, partially effective, moderately effective, and completely effective. These levels of effectiveness were not strictly defined. Some survey questions allowed for "free-text" answers in order to account for drugs, effects, reactions, doses, and regimens that were not included in the standardized answer choices. Three questions were "free-text" only and six included a comment section where responses could be elaborated using "free-text." There were a total of 651 responders, 558 of whom completed the survey. Of the completers, 496 indicated that their diagnosis of cluster headache was verified by a neurologist or headache specialist. All further analysis was made from this pool of 496 validated responders. This number is within range of other survey studies (n = 53–1134) (Klapper, Klapper, and Voss 2000; Rozen and Fishman 2012; Sewell, Halpern, and Pope 2006).

Statistical Analysis

The majority of the data are descriptive. Inferences on single proportions were calculated to determine the statistical difference between two percentages. Different formulae were used for single- and dual-population calculations. Survey participants scaled the efficacy of medications as not effective, partially, moderately, or completely. Lesser and greater levels of efficacy were compared via Fisher's exact test using GraphPad software. Specifically, the number reporting "not effective + partially effective" were compared against the number reporting "moderately effective + completely effective."

RESULTS

Demographics and Headache Characteristics

Demographic data are shown in Table 1. Both men (366, 73.8%) and women (130, 26.2%) from various global regions and ethnic backgrounds were included in the survey. Cluster headache in the immediate family did not differ between men (56, 15.2%) and women (19, 14.8%; $p > 0.5$). The onset of cluster headache was more common in earlier decades, though the time to diagnosis from

TABLE 1
Demographic Information

	N (Percentage)
Gender	
Male	366 (73.8)
Female	130 (26.2)
Race	
Caucasian	462 (93.1)
Hispanic	13 (2.6)
Black	6 (1.2)
Asian	4 (<1.0)
Other	9 (1.8)
No response	2 (<1.0)
Global region	
United States	310 (62.5)
Europe	58 (11.6)
United Kingdom	58 (11.6)
Canada	25 (5.0)
Africa	1 (<1.0)
Asia	3 (<1.0)
Other	41 (8.2)
Family history of cluster headache (first-degree relatives)	
Yes	75 (15.1)
No	359 (72.4)
Unsure	2 (12.5)
Age at time of survey	
<21	3 (<1.0)
21–30	55 (11.1)
31–40	133 (26.8)
41–50	146 (29.4)
51–60	117 (23.6)
61–70	39 (7.9)
>70	3 (<1.0)
Age of onset of cluster headache	
<21	170 (34.2)
21–30	153 (30.8)
31–40	91 (18.3)
41–50	61 (12.3)
51–60	18 (3.6)
>60	3 (<1.0)
Time from onset to diagnosis	
<6 months	41 (8.2)
<1 year	65 (13.1)
2 years	86 (17.3)
3–5 years	110 (22.2)
6–10 years	97 (19.6)
>10 years	97 (19.6)

first cluster attack ranged widely. The age of onset did not differ between gender (data not shown), but more women (36, 27.7%) than men (63, 17.2%) were diagnosed within one year of their first cluster attack ($p < 0.02$).

Data on headache characteristics are shown in Table 2. Both primary episodic (313, 63.1%) and primary chronic (77, 15.5%) cluster headache types were included in the survey. The remaining started with one type and converted to another (secondary cluster headache) or were unsure of their classification. Neither age of onset nor time to diagnosis differed between headache type at time of onset (data not shown). The majority of survey responders (421,

TABLE 2
Headache Characteristics

	N (Percentage)
Subtype	
Primary Episodic	313 (63.1)
Primary Chronic	77 (15.5)
Secondary Episodic (formerly chronic)	20 (4.0)
Secondary Chronic (formerly episodic)	78 (15.7)
Uncertain	8 (1.6)
Number of attacks a day	
1–3	250 (50.4)
4–6	171 (34.5)
7–15	68 (13.7)
≥16	7 (1.4)
Laterality in episodic cluster headache (n = 333)	
Right	147 (44.1)
Left	120 (36.0)
Other	7 (2.1)
Within period	
Right (some left)	11 (3.3)
Left (some right)	14 (4.2)
Between periods	
Right (switch to left)	21 (6.3)
Left (switch to right)	13 (3.9)
Laterality in chronic cluster headache (n = 155)	
Right	62 (40.0)
Left	47 (30.3)
Right (some left)	26 (16.8)
Left (some right)	15 (9.7)
Other	5 (3.2)
Length of periods (episodic) (n = 337)	
<4 weeks	21 (6.2)
4–6 weeks	73 (21.7)
7–8 weeks	55 (16.3)
9–12 weeks	72 (21.4)
13–16 weeks	42 (12.5)
>16 weeks	57 (16.9)
Unsure/insufficient history	17 (5.0)
Remission periods in episodic cluster headache (n = 343)	
<6 months	89 (25.9)
7 months—1 year	107 (31.2)
≤2 years	84 (24.5)
≤3 years	33 (9.6)
>3 years	17 (5.0)
Unsure/insufficient history	13 (3.8)
Remission periods in chronic cluster headache (n = 165)	
1–2 days	32 (19.4)
3–4 days	18 (10.9)
5–6 days	15 (9.1)
7–14 days	36 (21.8)
>14 days	64 (38.8)

84.9%) had fewer than seven attacks daily. In episodics, there were more right (147, 44.1%) than left (120, 36.0%) side-locked attacks ($p < 0.04$), whereas side-locked laterality was equal in chronics (right 62, 40.0%; left 47, 30.3%; $p > 0.05$). When side-locked and side-predominant attacks are combined, attacks were more common on the

right in both episodics (right 179, 53.8%; left 147, 44.1%; $p < 0.02$) and chronics (right 88, 56.8%; left 62, 40.0%; $p < 0.005$).

Abortive Medications

The medications most commonly used to abort cluster attacks along with their relative efficacies are illustrated in Figure 1. Specific comparisons on the most effective medications are described in the following; each medication is followed by the n for lesser and greater levels of efficacy, respectively. Triptan injection (subcutaneous; 64, 232) was more effective than high-flow oxygen (126, 262; $p < 0.002$), triptan pills (211, 104; $p < 0.0001$), intranasal triptan (157, 111; $p < 0.0001$), and psilocybin (53, 93; $p < 0.002$). High-flow oxygen was more effective than triptan pills ($p < 0.0001$) and intranasal triptan ($p < 0.0001$), but no more effective than psilocybin ($p > 0.4$). Psilocybin was significantly more effective than triptan pills ($p < 0.0001$) and intranasal triptan ($p < 0.0001$). Other compounds in the indoleamine class, cafergot/ergotamine (127, 44) and intravenous dihydroergotamine (DHE; 34, 28), were significantly less effective than high-flow oxygen ($p < 0.001$, $p < 0.0001$), triptan injection (both $p < 0.0001$), and psilocybin ($p < 0.0001$, $p < 0.02$).

Preventative Medications

The medications most commonly used to prevent cluster attacks along with their relative efficacies are illustrated in Figure 2. Specific comparisons on the most effective medications are described in the following; each medication is followed by the n for lesser and greater levels of efficacy, respectively. Prednisone (167, 145) was significantly more effective than verapamil (232, 132; $p < 0.008$). Psilocybin (52, 129), LSD (16, 58), and lysergic acid amide (LSA; 44, 64) were significantly more effective than verapamil (all $p < 0.0001$), prednisone ($p < 0.0001$, $p < 0.0001$, $p < 0.03$), and the non-hallucinogenic indoleamine, methysergide (88, 19; all $p < 0.0001$). Psilocybin was not statistically different from LSD ($p > 0.2$) or its non-hallucinogenic congener, 2-bromo-lysergic acid diethylamide (BOL or BOL-148; 4, 6; $p > 0.4$), but was statistically more effective than LSA ($p < 0.04$) and the other indoleamine hallucinogen, dimethyltryptamine (DMT; 10, 8; $p < 0.04$). LSD was statistically similar in effectiveness to BOL ($p > 0.2$), but was significantly more effective than LSA ($p < 0.01$) and DMT ($p < 0.008$). LSA was statistically similar to BOL ($p > 0.9$) and DMT ($p > 0.3$). BOL was statistically similar in effectiveness to verapamil ($p > 0.1$), prednisone ($p > 0.5$), and DMT ($p > 0.6$), but was significantly more

FIGURE 1
Abortive Medications (Number Who Tried, % of Total)

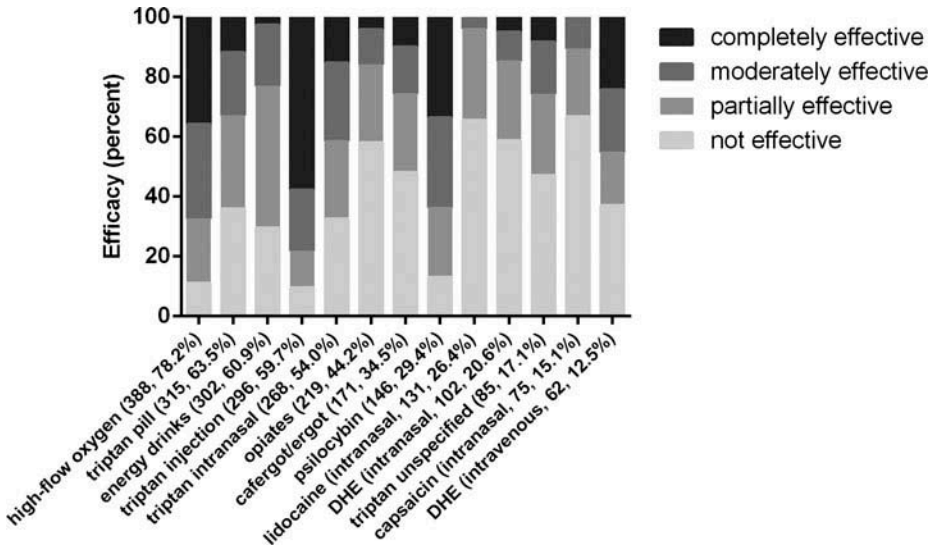
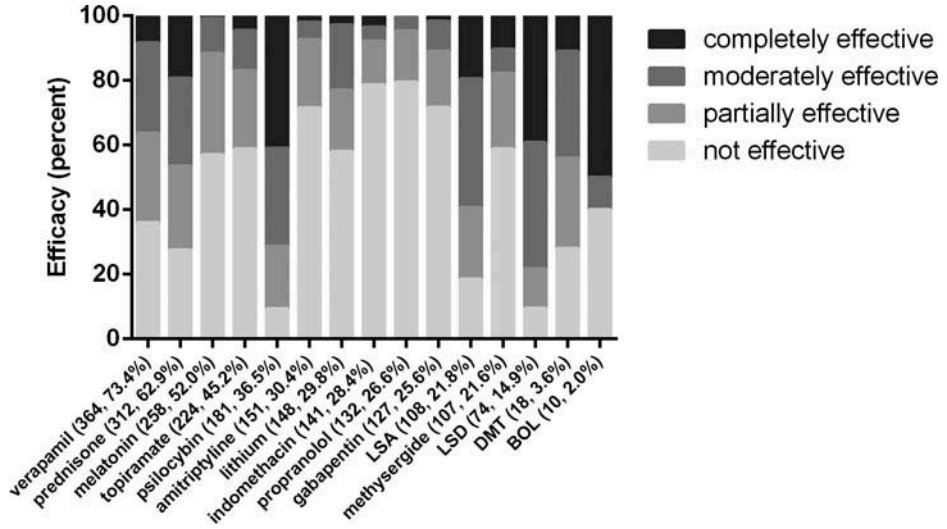


FIGURE 2
Preventative Medications (Number Who Tried, % of Total)



effective than methysergide ($p < 0.006$). DMT was as effective as prednisone ($p > 0.9$) and verapamil ($p > 0.4$).

Effects on the Cluster Period, Remission, and Conversion

Many survey responders specified which medications, treatments, or situations shortened or aborted a cluster period. These free-texted answers often included more than a single response and thus, from 199 responders, there were 264 distinct responses. In order of decreasing prevalence, these included psilocybin (67, 33.7%), verapamil (33, 16.6%), LSA (32, 16.1%), steroids (30, 15.1%), LSD (13, 6.5%), vitamin regimen (7, 3.5%), topiramate (4, 2.0%), lithium (3, 1.5%), and BOL (2, 1.0%). The percentage of those who identified psilocybin here was significantly greater than all other responses (all $p < 0.001$). The percentage of those who identified LSD was significantly less than either verapamil ($p < 0.002$) or steroid ($p < 0.01$), while LSA was no different from these two traditional medications (both $p > 0.5$).

Many survey responders felt there was a medication, treatment, or situation that led to remission from chronic cluster headache. These free-texted answers often included more than a single response and thus, from the 60 responders, there were 80 distinct responses. In order of decreasing prevalence, these included psilocybin (18, 30.0%), LSA (8, 13.3%), verapamil (7, 11.7%), LSD (6, 10.0%), steroids (3, 5.0%), topiramate (3, 5.0%), vitamin regimen (3, 5.0%), and lithium (1, 1.7%). The percentage of those who identified psilocybin here was significantly greater than all other responses, specifically: verapamil ($p < 0.02$), steroid ($p < 0.001$), LSD ($p < 0.005$), and LSA ($p < 0.04$). Neither LSD nor LSA was different from either verapamil or steroid. Of note, the vitamins identified in the free-text portions of the survey included vitamin D, riboflavin, magnesium, calcium, omega 3, zinc, and boron.

For those survey responders who were previously episodic and became chronic (secondary chronic), various medications were being taken at the time of transition. These free-texted answers often included more than a single response and thus, from the 75 responders, there were 164 distinct responses. In order of decreasing prevalence, these included verapamil (40, 53.3%), triptans (25, 33.3%), lithium (10, 13.3%), opiates (10, 13.3%), oxygen (9, 12.0%), steroids (8, 10.7%), topiramate (8, 10.7%), no medication (6, 8.0%), valproate (6, 8.0%), cafergot (5, 6.7%), tricyclic antidepressant (4, 5.3%), barbiturate (2, 2.7%), pregabalin (2, 2.7%), psilocybin (2, 2.7%), benzodiazepines (1, 1.3%), DHE (1, 1.3%), LSA (1, 1.3%), and LSD (1, 1.3%). By percentage, psilocybin, LSD, and LSA were identified significantly less often than half the other drugs (data not shown).

Dosing and Regimens

Within the free-text sections of the survey, participants were asked to state the dose and frequency of their most effective abortive and preventative medications. The

commonly used preventative medication, verapamil, was effective between 120 and 1020 mg daily (n = 84). The most commonly reported dose was 480 mg daily (n = 18), which is the maximum typically prescribed. Fully one-third of the reported verapamil doses were over 480 mg daily. While hallucinogen doses were relatively consistent among responders, some listed a certain number of pills, tabs, capsules, drops, seeds, or mushrooms that could not be converted to a precise dose. For those who clearly indicated a weight dose, psilocybin in the form of dried mushrooms was used for abortive purposes from 0.1 to 5 gm (n = 14) and for prevention from 0.1 to 6 gm (n = 57). These are within (and some below) the reported recreational dose range of 0.5 to 25 gm (Erowid 2011; Passie et al. 2002). The doses of LSD for aborting (150 to 200 μg; n = 2) and preventing (100–300 μg; n = 8) attacks were on the higher end of the recreational range of 50–200 μg (Erowid 2002; Nichols 2004). The doses of LSA are more difficult to estimate given that the number of seeds consumed varies among the plant varieties: *Turbina (Rivea) corymbosa* (14–300), *Argyreia nervosa* (3–10), and *Ipomoea violacea* or morning glory (50–500) (Erowid 1994, 1993; Halpern 2004; Isbell and Gorodetzky 1966). For abortive purposes, 4–50 seeds (n = 6) were reported; 2–300 seeds (n = 29) for attack prevention. The only BOL regimen reported (3.1 mg every five days for three days; n = 1) corresponds to that used in an earlier case series (Karst et al. 2010). Psilocybin, LSD, and LSA, along with another hallucinogen, DMT, were used daily to weekly for abortive purposes (n = 23). For prevention, they were used every few weeks to twice yearly (n = 80). The word "single" or "once" to indicate one dose of psilocybin or LSD was clearly written by eight responders.

Side-Effects

Though side-effects were not specifically queried, a few participants (less than 30) noted them in the free-text sections. Sumatriptan, cafergot, and steroids led to rebound headaches. Of course, as this term was not defined, it may be difficult to distinguish a rebound headache from a new cluster attack. The narcotics meperidine and codeine-paracetamol caused nausea and vomiting. Verapamil led to swelling, hypotension, and cardiac arrhythmias. Gabapentin caused memory loss in one participant, while topiramate reduced sexual drive in another. Prednisone caused mania and led to avascular necrosis of the femur in one responder. Other medications described as having intolerable "side-effects" were lithium, zonisamide, and eletriptan. In contrast, there was little mention of negative effects for indoleamine hallucinogens. LSD caused headache in one individual. LSA gave a "sickness" and "wooziness" when initially tried by another. LSA also led to abdominal discomfort in one participant, who also had irritable bowel syndrome.

DISCUSSION

Cluster headache is a neglected condition despite prevalence and burden similar to that of more familiar neurologic diseases (e.g., multiple sclerosis). There is only one drug approved by the Food and Drug Administration for cluster headache: subcutaneous sumatriptan. As such, any discussion or survey of treatments in cluster headache includes primarily off-label use of approved drugs or unapproved therapies of other types. The Clusterbusters medication use survey considered both conventional and alternative therapies. The findings are consistent with earlier evidence that indoleamine hallucinogens are effective agents for the treatment of cluster headache (Matharu et al. 2005; Sewell, Halpern, and Pope 2006). Other findings, such as gender, family history, age of onset, and attack laterality, are comparable to those reported in prior research. (Bahra and Goadsby 2004; Klapper, Klapper, and Voss 2000; Manzoni et al. 1983; Rozen and Fishman 2012; Schurks et al. 2006; Sewell, Halpern, and Pope 2006; Xie et al. 2013).

High-flow oxygen and triptan injections were the most commonly used and effective abortive treatments in the current survey, as is consistently reported in the literature (Anonymous 1991; Cohen, Burns, and Goadsby 2009; Klapper, Klapper, and Voss 2000; Schurks et al. 2006). Psilocybin was tried as an abortive therapy in roughly one-third of responders; two-thirds of that group found it to be at least moderately effective and one-third completely effective. At both levels of efficacy, psilocybin was comparable to high-flow oxygen and better than oral and intranasal triptan, but less effective than injectable triptan. Of course, as cluster attacks may be as short as 15 minutes, medication mode of administration is highly relevant. In the acute treatment of cluster attacks, high-flow oxygen was found to abort the majority attacks within 15 minutes in over 80% of subjects (Kudrow 1981). Subcutaneous sumatriptan injection led to pain freedom in 46% of subjects after 15 minutes and 77% after 30 minutes (The Sumatriptan Cluster Headache Study Group 1991). Intranasal sumatriptan (20 mg) produced pain freedom in only 16% of subjects after 15 minutes and approximately half after 30 minutes (Schuh-Hofer et al. 2002; Van Vliet et al. 2003). Similarly, oral zolmitriptan (both 5 mg and 10 mg) led to mild or no pain after 30 minutes in approximately half of subjects (Bahra et al. 2000). The reported superiority of oral psilocybin against other oral, intranasal, and inhaled medications in this survey suggests that it is an effective abortive agent in cluster headache. Of note, LSD and LSA, which are discussed in preventative efficacy, were not included in the list of drug options for abortive medications.

The most commonly used preventive medications in the current survey included verapamil, prednisone, melatonin, topiramate, and psilocybin. The first two

medications afforded at least partial effectiveness in 64.0% and 72.4% of those who tried them, respectively. This is similar to other surveys that reported preventative efficacies of about 60% for verapamil and about 70% for steroids (Klapper, Klapper, and Voss 2000; Schurks et al. 2006). Of note, steroids are technically not used as a preventative in cluster headache, but rather as an agent to induce remission. Thus, we acknowledge the imprecise interpretation of steroids as a preventative in this survey. The efficacy of topiramate, lithium, and melatonin as preventatives was also roughly comparable to previous reports (Klapper, Klapper, and Voss 2000; Leone et al. 1996; Schurks et al. 2006). In contrast to these conventional medications, the current study shows that psilocybin and LSD provided over 70% of those who tried them with at least moderate protection from attacks. Complete preventative efficacy was about 40% for each drug, which is greater than that reported for any other conventional medication. Though only 10 survey responders tried BOL, this non-hallucinogenic congener of LSD provided at least moderate protection from attacks in 60% of those who tried it. Similarly, the case series of BOL in cluster headache reported dramatic effect in attack frequency and intensity in four out of five subjects (Karst et al. 2010). The preventative effect of BOL in the current survey was similar to both psilocybin and LSD, even when comparing at the level of complete efficacy. The current study might suggest that some indoleamine compounds, both hallucinogenic and non-hallucinogenic, could be effective in cluster attack prevention.

Interestingly, participants in the present survey described relatively infrequent use of hallucinogens for the treatment of cluster headache—between every few weeks to twice yearly. These regimens distinguish these compounds from other preventive medications that require daily dosing and have many negative side-effects. Several participants in the current survey also reported that a single dose of psilocybin or LSD prevented attacks, shortened/aborted a cluster period, or induced remission from chronic cluster headache. While limited by small number and uncontrolled variables, this effect of single dosing is noted. A single or few doses of psilocybin, LSD, and BOL were previously reported to induce remission or act as a preventive cluster headache medication (Karst et al. 2010; Matharu et al. 2005; Sewell, Halpern, and Pope 2006). The ability of single-dose LSD to treat alcoholism was reported over half a century ago (Krebs and Johansen 2012). Studies are underway to investigate the effects of psilocybin in drug addiction therapy. (Ross 2012). Psilocybin has also treated anxiety in cancer patients, obsessive-compulsive symptoms, and affected attitude, mood, and behavior after a single or few doses (Griffiths et al. 2011; Grob et al. 2011; Moreno et al. 2006).

Another consideration raised in the current survey is the role for hallucinogenesis in the therapeutic effect of indoleamines. The doses of psilocybin, LSD, and LSA reported in this survey were largely within the recreational range, though participants used sub-hallucinogenic doses of psilocybin. In a previous cluster headache survey, 42% of participants found sub-hallucinogenic doses of psilocybin and LSD to be effective (Sewell, Halpern, and Pope 2006). While the non-hallucinogenic ergot derivative, methysergide, was not particularly effective in this survey, the non-hallucinogenic LSD congener, BOL, was on par with psilocybin, LSD, and LSA in preventative efficacy. Thus, while the pharmacological substrate for hallucinogens' unique effects in cluster headache and other medical conditions remains unknown, early evidence would suggest that hallucinogenesis itself is not required for the actions of indoleamine hallucinogens on cluster headache (Karst et al. 2010; Sewell, Halpern, and Pope 2006).

This study has several limitations. As the survey was only available online, there is bias for those with Internet access and who visited the participating websites, which also include information about alternative therapies. There is bias for those who are aware of non-traditional medications as well as those who are refractory to more conventional therapies. There is also recall bias, particularly for those with decades of history of cluster headache. Furthermore, there is lack of diagnostic validity, although only those responders who vouched for their diagnosis by a medical specialist were included. Some of the survey responders indicated they had over 16 cluster attacks daily, whereas the International Classification of Headache Disorders IIIb criteria indicate that there be up to eight cluster attacks per day (Headache Classification Committee of the International Headache 2013). Given the limitation of diagnostic validity, this high number of attacks posits that these participants may have another type of headache, including paroxysmal hemicranias or SUNCT (short-lasting unilateral neuralgiform headache) (Headache Classification Committee of the International Headache 2013). In addition, the four levels of efficacy were not clearly defined in this survey, allowing for individual interpretation of efficacy among participants. Furthermore, as many survey responders tried multiple drugs, the comparisons of effectiveness are not truly from independent samples. Finally, medication dosing and purity could not be verified in this survey, neither for prescribed nor for illicit substances (Okie 2009; Schnoll and Vogel 1971).

CONCLUSION

The Clusterbusters medication use survey further supports the efficacy of indoleamine hallucinogens, such as psilocybin, LSD, and LSA, in the treatment of cluster headache. This survey considered effects beyond the cluster attack itself, including shortening/aborting a cluster period and transitioning from chronic to episodic cluster headache. Importantly, this survey also demonstrated that the indoleamine hallucinogens effected clinical relief with modest and infrequent use. This work follows similar reports of safety and efficacy of these compounds in varying medical applications (Griffiths et al. 2011; Grob et al. 2011; Krebs and Johansen 2012; Moreno et al. 2006; Ross 2012). A controlled study will be required to establish the effects of indoleamine hallucinogens in cluster headache. Though these drugs are historically safe (Nichols 2004), the non-hallucinogen BOL, which has demonstrated efficacy in cluster headache (Karst et al. 2010), would provide the opportunity to explore the effects of this unique pharmacologic class independent of hallucinogenesis.

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REFERENCES

Anonymous. 1991. Treatment of acute cluster headache with sumatriptan. The sumatriptan cluster headache study group. *New England Journal of Medicine* 325 (5):322–26. doi:10.1056/NEJM199108013250505.

Bahra, A., M. J. Gawel, J.-E. Hardebo, D. Millson, S. A. Breen, and P. J. Goadsby. 2000. Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 54 (9):1832–39. doi:10.1212/WNL.54.9.1832.

Bahra, A., and P. J. Goadsby. 2004. Diagnostic delays and mismanagement in cluster headache. *Acta Neurologica Scandinavica* 109 (3):175–79.

Cohen, A. S., B. Burns, and P. J. Goadsby. 2009. High-flow oxygen for treatment of cluster headache: A randomized trial. *Jama* 302 (22):2451–57.

Cohen, A. S., and P. J. Goadsby. 2006. Functional neuroimaging of primary headache disorders. *Expert Review of Neurotherapeutics* 6 (8):1159–71. doi:10.1586/14737175.6.8.1159.

Erowid. 1993. Natural highs FAQ. http://www.erowid.org/psychoactives/faqs/natural_highs_faq.shtml.

Erowid. 1994. The complete morning glory FAQ. http://www.erowid.org/plants/morning_glory/morning_glory_faq.shtml.

Erowid. 2002. LSD FAQ. http://www.erowid.org/chemicals/lsd/lsd_faq.shtml.

Erowid. 2011. Psilocybe mushroom FAQ. http://www.erowid.org/plants/mushrooms/mushrooms_faq.shtml.

Griffiths, R. R., M. W. Johnson, W. A. Richards, B. D. Richards, U. McCann, and R. Jesse. 2011. Psilocybin occasioned mystical-type experiences: Immediate and persisting dose-related effects. *Psychopharmacology (Berl)* 218 (4):649–65. doi:10.1007/s00213-011-2358-5.

Grob, C. S., A. L. Danforth, G. S. Chopra, M. Hagerty, C. R. McKay, A. L. Halberstadt, and G. R. Greer. 2011. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Archives of General Psychiatry* 68 (1):71–78. doi:10.1001/archgenpsychiatry.2010.116.

Halpern, J. H. 2004. Hallucinogens and dissociative agents naturally growing in the United States. *Pharmacology & Therapeutics* 102 (2):131–38. doi:10.1016/j.pharmthera.2004.03.003.

Headache Classification Committee of the International Headache, S. 2013. The international classification of headache disorders, 3rd edition (beta version). *Cephalalgia* 33 (9):629–808. doi:10.1177/0333102413485658.

Horton, B. T. 1952. Histaminic cephalgia. *The Lancet* 72 (2):92–98.

Isbell, H., and C. W. Gorodetzky. 1966. Effect of alkaloids of ololiuqui in man. *Psychopharmacologia* 8 (5):331–39. doi:10.1007/BF00453511.

Karst, M., J. H. Halpern, M. Bernateck, and T. Passie. 2010. The non-hallucinogen 2-bromo-lysergic acid diethylamide as preventative treatment for cluster headache: An open, non-randomized case series. *Cephalalgia* 30 (9):1140–44. doi:10.1177/0333102410363490.

Klapper, J. A., A. Klapper, and T. Voss. 2000. The misdiagnosis of cluster headache: A nonclinic, population-based, Internet survey. *Headache* 40 (9):730–35. doi:10.1046/j.1526-4610.2000.00127.x.

Krebs, T. S., and P.-O. Johansen. 2012. Lysergic acid diethylamide (LSD) for alcoholism: Meta-analysis of randomized controlled trials. *Journal of Psychopharmacology* 26 (7):994–1002. doi:10.1177/0269881112439253.

Kudrow, L. 1981. Response of cluster headache attacks to oxygen inhalation. *Headache* 21 (1):1–4. doi:10.1111/hed.1981.21.issue-1.

Leone, M., D. D'Amico, F. Moschiano, F. Fraschini, and G. Bussone. 1996. Melatonin versus placebo in the prophylaxis of cluster headache: A double-blind pilot study with parallel groups. *Cephalalgia* 16 (7):494–96. doi:10.1046/j.1468-2982.1996.1607494.x.

Magis, D., and J. Schoenen. 2012. Advances and challenges in neurostimulation for headaches. *The Lancet Neurology* 11 (8):708–19. doi:10.1016/S1474-4422(12)70139-4.

Manzoni, G. C., M. G. Terzano, G. Bono, G. Micieli, N. Martucci, and G. Nappi. 1983. Cluster headache: Clinical findings

in 180 patients. *Cephalalgia* 3 (1):21–30. doi:10.1046/j.1468-2982.1983.0301021.x.

Matharu, M. S., J. A. Van Vliet, M. D. Ferrari, and P. J. Goadsby. 2005. Verapamil induced gingival enlargement in cluster headache. *Journal of Neurology, Neurosurgery & Psychiatry* 76 (1):124–27. doi:10.1136/jnnp.2003.024240.

May, A. 2005. Cluster headache: Pathogenesis, diagnosis, and management. *The Lancet* 366 (9488):843–55. doi:10.1016/S0140-6736(05)67217-0.

Moreno, F. A., C. B. Wiegand, E. K. Taitano, and P. L. Delgado. 2006. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *The Journal of Clinical Psychiatry* 67 (11):1735–40. doi:10.4088/JCP.v67n1110.

Nichols, D. E. 2004. Hallucinogens. *Pharmacology & Therapeutics* 101 (2):131–81. doi:10.1016/j.pharmthera.2003.11.002.

Okie, S. 2009. Multinational medicines: Ensuring drug quality in an era of global manufacturing. *The New England Journal of Medicine* 361 (8):737–40. doi:10.1056/NEJMp0903870.

Passie, T., J. Seifert, U. Schneider, and H. M. Emrich. 2002. The pharmacology of psilocybin. *Addiction Biology* 7 (4):357–64. doi:10.1080/1355621021000005937.

Robbins, M. S. 2013. The psychiatric comorbidities of cluster headache. *Current Pain and Headache Reports* 17 (2):313. doi:10.1007/s11916-012-0313-8.

Ross, S. 2012. Serotonergic hallucinogens and emerging targets for addiction pharmacotherapies. *Psychiatric Clinics of North America* 35 (2):357–74. doi:10.1016/j.psc.2012.04.002.

Rozen, T. D., and R. S. Fishman. 2012. Cluster headache in the United States of America: Demographics, clinical characteristics, triggers, suicidality, and personal burden. *Headache: The Journal of Head and Face Pain* 52 (1):99–113. doi:10.1111/j.1526-4610.2011.02028.x.

Schnoll, S. H., and W. H. Vogel. 1971. Analysis of "street drugs." *The New England Journal of Medicine* 284 (14):791. doi:10.1056/NEJM197104082841414.

Schoenen, J., L. Di Clemente, M. Vandenheede, A. Fumal, V. De Pasqua, M. Mouchamps, J. M. Remacle, and A. M. De Noordhout. 2005. Hypothalamic stimulation in chronic cluster headache: A pilot study of efficacy and mode of action. *Brain* 128 (Pt 4):940–47. doi:10.1093/brain/awh411.

Schuh-Hofer, S., U. Reuter, S. Kinze, K. M. Einhäupl, and G. Arnold. 2002. Treatment of acute cluster headache with 20 mg sumatriptan nasal spray: An open pilot study. *Journal of Neurology* 249 (1):94–99. doi:10.1007/PL00007854.

Schurks, M., T. Kurth, J. De Jesus, M. Jonjic, D. Rosskopf, and H.-C. Diener. 2006. Cluster headache: Clinical presentation, lifestyle features, and medical treatment. *Headache* 46 (8):1246–54. doi:10.1111/hed.2006.46.issue-8.

Sewell, R. A., J. H. Halpern, and H. G. Pope, Jr. 2006. Response of cluster headache to psilocybin and LSD. *Neurology* 66 (12):1920–22. doi:10.1212/01.wnl.0000219761.05466.43.

Starr, P. A., N. M. Barbaro, N. H. Raskin, and J. L. Ostrem. 2007. Chronic stimulation of the posterior hypothalamic region for cluster headache: Technique and 1-year results in four patients. *Journal of Neurosurgery* 106 (6):999–1005. doi:10.3171/jns.2007.106.6.999.

The Sumatriptan Cluster Headache Study Group. 1991. Treatment of acute cluster headache with sumatriptan. *The New England Journal of Medicine* 325 (5):322–26. doi:10.1056/NEJM199108013250505.

Van Vliet, J. A., A. Bahra, V. Martin, N. Ramadan, S. K. Aurora, N. T. Mathew, M. D. Ferrari, and P. J. Goadsby. 2003. Intranasal sumatriptan in cluster headache: Randomized placebo-controlled double-blind study. *Neurology* 60 (4):630–33. doi:10.1212/01.WNL.0000046589.45855.30.

Xie, Q., Q. Huang, J. Wang, N. Li, G. Tan, and J. Zhou. 2013. Clinical features of cluster headache: An outpatient clinic study from China. *Pain Medicine* 14 (6):802–07. doi:10.1111/pme.12101.