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Abstract—The authors interviewed 53 cluster headache patients who had used psilocybin or lysergic acid diethylamide (LSD) to treat their condition. Twenty-two of 26 psilocybin users reported that psilocybin aborted attacks; 25 of 48 psilocybin users and 7 of 8 LSD users reported cluster period termination; 18 of 19 psilocybin users and 4 of 5 LSD users reported remission period extension. Research on the effects of psilocybin and LSD on cluster headache may be warranted.

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Cluster headache, often considered the most painful of all types of headache,[1] affects predominantly men (0.4% vs 0.08% of women) and typically begins after age 20 years. The disorder is categorized as either *episodic*, occurring for 1-week to 1-year periods, interspersed with pain-free remission periods, or *chronic*, in which the headaches occur constantly for more than a year with no remission longer than 1 month.[2] Ten percent of episodic cluster headaches ultimately evolve into the chronic form, and these are termed *secondary chronic*. In standard descriptions of cluster headache, an *attack* refers to the actual paroxysm of pain, a *cluster period* refers to a period of time when attacks occur regularly, and a *remission period* refers to a prolonged attack-free interval.[3] Oxygen and sumatriptan are the mainstays of acute abortive treatment, whereas verapamil, lithium, corticosteroids, and other neuromodulators can suppress attacks during cluster periods. No medications are known to terminate cluster periods or extend remission periods. The effects of the ergot alkaloid derivative lysergic acid diethylamide (LSD) and the related indolalkylamine psilocybin on cluster headache have not previously been described and may include such properties.

Case series. We were contacted by a 34-year-old man, diagnosed with episodic cluster headache at age 16 years, who reported a complete remission of his cluster periods when he repeatedly used LSD on a recreational basis between ages 22 and 24 years. Cluster periods resumed once he stopped. Based on this experience, he attempted to treat his cluster headache by ingesting psilocybin-containing mushrooms every 3 months and again achieved lasting remission. On three occasions when he missed his scheduled dose, a cluster period reoccurred.

Intrigued by this history, we located—through cluster headache support groups and an Internet-based survey—several hundred people with cluster headache who reported use of psilocybin-containing mushrooms or LSD specifically to treat their disorder, and we administered a standardized questionnaire (available from the authors). The consent form and study were approved by the McLean Hospital institutional review board. We restricted our analysis to the 53 individuals who 1) agreed to be contacted for evaluation by telephone or e-mail and 2) met International Classification of Headache Disorders-2 criteria for cluster headache and allowed us to obtain copies of medical records documenting a diagnosis of cluster headache by an MD or DO. If the medical records did not support the diagnosis, the subject was excluded from further analysis. The final sample included subjects from across the United States as well as Great Britain, The Netherlands, and South Africa. We found no significant differences between men and women on demographic indices or headache features (table 1). Notably, 31 (58%) of the 53 individuals reported that they had never used psilocybin or LSD except to treat their cluster headache, and a further 13 (25%) had used these drugs for recreational purposes only in the remote past during adolescence.

Results are summarized in table 2 and listed in complete form in table E-1 (on the *Neurology* Web site at www.neurology.org). Of the 32 subjects with episodic cluster headache, 19 had used sublingual psilocybin during cluster attacks; 17 found psilocybin to be effective in aborting attacks (defined as ending the attack within 20 minutes). Only one subject had used sublingual LSD for an acute attack, reporting it to be effective. Twenty-nine subjects had used psilocybin prophylactically during a cluster period; 15 (52%) reported that it was effective (defined as causing total cessation of attacks), and a further 12 (41%) reported partial efficacy (defined as attacks decreasing in intensity or frequency but not ceasing). Five of six LSD users reported cluster period termination. Twenty subjects ingested psilocybin during a remission period; 19 reported an extension of their remission period, in that their next expected cluster period was delayed or prevented entirely. Four of five subjects reported similar remission extension with LSD.

Of the 21 subjects with chronic cluster headache, 5 of 7 reported that psilocybin aborted a cluster attack; 10 of 20 reported that psilocybin induced a complete termination of cluster attacks; and a further 8 reported partial efficacy. Of two chronic cluster headache patients who ingested LSD, both at subhallucinogenic doses, one reported no attacks for 10 days, and the other reported none for 2 months. Interestingly, 22 (42%) of the 53 subjects reported partial or complete efficacy (as defined above) from subhallucinogenic doses of psilocybin or LSD.

Discussion. Our results are interesting for three reasons. First, no other medication, to our knowledge, has been reported to terminate a cluster period. Second, unlike other ergot-based medications, which must be taken daily, a single dose of LSD was described as sufficient to induce remission of a clus-

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Table 1 *Cluster headache characteristics by sex and subtype*

Headache type	n	Age, y	Headache features			
			Attack duration, min	Attacks/day at peak	Cluster period duration, wk	Remission period duration, wk
Episodic						
Men	26	45 (8)	97 (66)	5.5 (3.7)	13 (10)	11 (10)
Women	6	45 (11)	66 (34)	6.2 (3.0)	15 (10)	9 (5)
Total	32	45 (8)	91 (60)	5.6 (3.5)	13 (10)	11 (9)
1° Chronic					NA	NA
Men	6	48 (8)	79 (57)	9.8 (7.4)		
Women	1	38 (NA)	90 (NA)	8.0 (NA)		
Total	7	47 (8)	81 (53)	9.6 (6.8)		
2° Chronic					NA	NA
Men	10	45 (6)	105 (70)	6.9 (3.0)		
Women	4	46 (10)	139 (64)	7.5 (1.0)		
Total	14	45 (7)	115 (68)	7.1 (2.5)		

Data are presented as mean (SD).

1° = primary; 2° = secondary; NA = not applicable.

ter period, and psilocybin rarely required more than three doses. Third, given the apparent efficacy of subhallucinogenic doses, these drugs might benefit cluster headache by a mechanism unrelated to their psychoactive effects.

Table 2 *Reported efficacy of principal reported treatments for cluster attacks, cluster periods, and remission extension*

Medication	Total, n	Effective, n (%)	Partially effective, n (%)	Ineffective, n (%)
Acute treatment				
Oxygen	47	24 (52)	19 (40)	4 (9)
Triptans	45	33 (73)	8 (18)	4 (9)
Psilocybin	26	22 (85)	0 (0)	4 (15)
LSD	2	1 (50)	0 (0)	1 (50)
Prophylactic				
Propanolol	22	0 (0)	2 (9)	20 (91)
Lithium	20	1 (5)	8 (40)	11 (55)
Amitriptyline	25	0 (0)	4 (16)	21 (84)
Verapamil	38	2 (5)	22 (58)	14 (37)
Prednisone	36	15 (45)	5 (14)	15 (42)
Psilocybin	48	25 (52)	18 (37)	3 (6)
LSD	8	7 (88)	0 (0)	1 (12)
Remission extension				
Psilocybin	22 (31)	20 (91)	NA	2 (9)
LSD	5 (7)	4 (80)	NA	1 (20)

Nine additional individuals had taken psilocybin and two additional had taken lysergic acid diethylamide (LSD) purposefully for remission extension but were not yet due for another cluster period at the time of our evaluation; hence, for them, efficacy could not be scored.

Several limitations of this study should be considered. First, it is subject to recall bias, because it relies primarily on participants' retrospective reports. However, 6 participants (11%) provided detailed headache diaries that corroborated their recall. In addition, 3 (6%) of the 53 participants tried psilocybin for the first time subsequent to consenting to participate in the study but before being questioned; 2 reported complete efficacy and 1 reported partial efficacy—a prospective response rate consistent with our retrospective findings.

A second consideration is the possibility of selection bias, in that individuals with a good outcome may have been more likely to participate. Recruitment over the Internet also selects for younger, more educated, and more motivated subjects,[4] likely leading to increased reported efficacy.

Third, participants were not blind to their treatment, raising the possibility of a placebo response. However, cluster headache is known to respond poorly to placebo; controlled trials have shown a placebo response of 0% to prophylactic medications such as verapamil,[5] capsaicin,[6] and melatonin,[7] and less than 20% to abortive medications such as sumatriptan.[8] Therefore, it seems unlikely that we would have found more than 50 cases of apparent response to psilocybin or LSD through placebo effects alone.

Our observations must be regarded as preliminary, in that they are unblinded, uncontrolled, and subject to additional limitations as described above. Therefore, our findings almost certainly overestimate the response of cluster headache to psilocybin and LSD and should not be misconstrued as an endorsement of the use of illegal substances for the self-treatment of cluster headache. However, given the high reported efficacy for this notoriously refrac-

tory condition, it is difficult to dismiss this series of cases as entirely artifactual. Further research is warranted.

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