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The non-hallucinogen 2-bromo-lysergic acid diethylamide as preventative treatment for cluster headache: An open, non-randomized case series

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Introduction

Cluster headache (CH) is a stereotyped primary headache characterized by strictly unilateral severe orbital or periorbital pain and categorized as either episodic or chronic (1,2). Its prevalence is 0.1% (3). Oxygen and sumatriptan are the treatments of choice for individual attacks, whereas verapamil, lithium, corticosteroids and other neuromodulators can suppress attacks during cluster periods (1). All standard medication treatments may be ineffective. Surgical treatment may be an option for medication non-responders, including deep brain (4) or occipital nerve stimulation (5). However, serious complications from brain surgery, including death, can occur (6).

An Internet survey of 53 CH patients reported on claims that psilocybin is better at aborting acute attacks than either oxygen or sumatriptan and that LSD and psilocybin are both better at triggering and extending remission than standard drugs (7). However, due to hallucinogenicity and the absence of established medical indication, these drugs are criminalized and placed within the most restrictive Schedule I of the Controlled Substances Act, which sanctions only limited research use. Although the hallucinogenic properties of LSD and psilocybin are undesirable from both regulatory and patient safety perspectives, it was unclear to us at the outset whether a non-hallucinogenic analog could also provide meaningful relief to CH patients. To address the question of whether the CH relief associated with these two structurally diverse compounds is related to the mechanisms triggering intoxication, we decided to investigate the efficacy of a non-hallucinogenic analog of LSD. LSD's hallucinogenic effects are completely lost when the double bond in the D ring is saturated and with substitution at R2 (e.g. by bromination in 2-bromo-LSD) (BOL-148) (8). BOL-148 has been studied in volunteers (up to 20 mg per os) (9) and in patients suffering from vascular headaches but not, apparently, in patients with CH (9,10). These past studies concluded that BOL-148 is non-toxic and non-hallucinogenic. Only very mild side effects, if any, have been observed, when given in the dose range used in our project (30 µg/kg/body weight) (9). No long-term behavioral or psychological effects from BOL-148 have been reported from past studies with more than 300 healthy, normal subjects (11), and 30 mg BOL-148 administered daily over four to five weeks failed to alter active psychosis in chronically ill schizophrenic women (12).

Case series

Patients referred to Hannover Medical School's Pain Clinic were identified with CH if they met the respective diagnostic criteria of the International Classification of Headache Disorders (2). All patients, who were seriously affected by the disease, were non-responders to verapamil (or could not tolerate its side effects at higher doses) and to some extent to other prophylactic medications as well, although not all medication alternatives (e.g. topiramate or prednisone), or more invasive procedures (e.g. intravenous dihydroergotamine or occipital nerve stimulator implantation), had been attempted.

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All patients signed an informed consent that declared their agreement to participate in this project on the compassionate use of BOL-148 for CH. It was approved by the local ethics committee in accordance with German law. Patients kept a standardized daily diary of CH symptoms (see www.clusterbusters.com for a copy) starting at least two weeks prior to BOL-148 administration. BOL-148 was manufactured by THC pharm GmbH (Frankfurt am Main, Germany). A purity of >99.2% was identified by high-performance liquid chromatography (HPLC) and other analytical tests. BOL-148 30 µg/kg/body weight was dissolved in distilled water and then given once every five days for a total of three doses per os. BOL-148 was administered in the presence of two of the authors (MK, TP). Alterations in consciousness, thought disturbances, and vital signs (blood pressure, heart rate) were measured during a three-to-four-hour observational period, as BOL-148 is typically active for two to three hours. Patients were asked to continue completing daily headache diaries for at least one month or until they experienced three days of attacks, starting a new cluster series.

Results are summarized in Table 1 and Figure 1. One patient (S2) with episodic CH, who was in an active attack period, and four patients with the chronic form participated. All but one patient (S1) had experienced symptoms for more than 10 years. Patient S2's cluster period terminated after BOL-148 with a long-lasting remission period of six months (at last follow-up) and continuing. Patients S3 and S5 reported pronounced reduction of attack frequency, including full remission for more than one month, indicating transition from a chronic to an episodic form. Cluster attacks resumed after a two-month remission for patient S5. In nine months since BOL-148 treatment, patient S3 describes ongoing remission of cluster period, reporting only a few solitary sporadic attacks. Patient S4 reported a profound reduction in attack frequency, although without one full month of remission and attack frequency increasing approximately six months after BOL-148 treatment. In addition, patients S3 and S4 found the pain intensity of remaining occasional attacks so improved that they no longer administered an acute intervention, as they had prior to BOL-148. Although patient S1 did not experience pronounced attack reduction similar to the other four patients, he indicated a decrease of attack intensity of about 30% within the first four months. It is likely relevant that patient S1 continued to drink alcohol (contrary to advice), a known and common trigger for attacks.

No changes to heart rate and blood pressure were observed during BOL-148 treatment. Most of the patients recorded some kind of ''flabby'' or ''light drunk'' feelings. Patient S2 noted a ''funny'' feeling, tense muscles, and sweaty palms. These mild subjective effects lasted from one to two hours. No visual hallucinations or distortions occurred, nor was there any evidence of delusional thinking or overt psychosis.

Discussion

The results show that three single doses of BOL-148 within 10 days can either break a CH cycle or considerably improve the frequency and intensity of attacks, even resulting in changing from a chronic to an episodic form, with remission extending for many months or longer. While for patients S3, S4, and S5 the remission is very likely due to BOL-148 treatment, for S1, who charted in his diary continued attacks with reduced pain, and S2, who suffered from episodic CH, the observed effects may also be due to the natural course of the disease, despite S1 and S2's impression that their cluster attack cycle improved in ways they had not experienced before BOL-148. Except for very mild alterations of subjective state and mild to no sympathetic reactions for about two hours, no other side effects were observed.

Sicuteri et al. used LSD and some of its derivatives (with BOL-148 among them) in the treatment of migraine and other vascular headaches (10). Because those studies were entwined with the task of identifying the pathophysiological mechanism of vascular headaches (13), they lack exact documentation and follow-up results of the exposed subjects. Especially considering the results we report, no evidence has been found that BOL-148 was administered specifically for active CH in these earlier trials. A sufferers-driven interest in the clinical effects of LSD and psilocybin for CH did not develop until recently, from anecdotal observations to Internet-based discussions to the published Internet survey (7) and subsequent science-media interest. Interestingly, those reports describe a single dose or a few doses resulting in long-lasting effects, which we now also demonstrate from BOL-148. Taken together and in regard to failure of other more direct explanations, especially for the long-range remission extension, these results indicate that BOL-148, psilocybin, and LSD may influence the expression of genes (epigenetics), which are responsible for the biological clock of the organism (14). However, prolonged administration of BOL-148 does not result in cross-tolerance to LSD (15). This, in turn, suggests that BOL-148's mechanism of action for CH is unrelated to those receptor systems thought to be involved with hallucinogenicity: 5-HT-1A and 5-HT-2A (16). Similarly, psilocybin and LSD's treatment effects for CH also, then, may have little to do with their capacity to induce hallucinogenic effects. The ergotamines (including BOL-148, LSD, dihyroergotamine, and methysergide) likely have positive treatment effects for CH through serotonin-receptor-mediated vasoconstriction. BOL-148 was

Table 1. Demographic data and clinical aspects

Subject	S1	S2	S3	S4	S5
Sex (M/F)	M	M	M	M	M
Age (years)	46	28	47	41	41
Body weight (kg)	83	68	106	105	74
Body height (cm)	180	168	188	195	174
Years of illness	3	10	10	33	32
Cranial side of attacks	Left	Right	Left (1999–2005) Right (since 2005)	Right	Right
Cluster headache form	Chronic	Episodic	Chronic since 2005	Chronic since 2001	Chronic since 2007
Attacks per week in the pre-assessment week	6	7	10	15	19
Mean intensity of attacks (VAS) in the pre-assessment week	8.4	8.3	5.5	6.4	7.0
Treatments (acute)	Sumatriptan 20 mg IN	100% oxygen 15 l/min	100% oxygen 15 l/min	100% oxygen 15 l/min Sumatriptan 6 mg SC	100% oxygen 15 l/min
Treatments (prophylactic)	Verapamil 240 mg/day*	Verapamil 240 mg/day*	Verapamil 240 mg/day* Frovatriptan PO (up to 2.5 mg TID)	Methysergide unknown dose (for 1 year) Prednisolone 80 mg (for 5 days) Verapamil 320 mg/day* (for 3 months) Lithium unknown dose (for 3 months)	Verapamil 960 mg/day (for several months) 4 cycles with prednisolone starting with a daily dose of 100 mg lithium 450 mg/d (for 14 days) Doxepine 10 mg/day (for several months)
BOL-148 (30 μg/kg) three times within 10 days (days 1, 5, and 10)	2.5 mg	2.0 mg	3.1 mg	3.1 mg	2.2 mg
Side effects	"Flabby feeling" for about 2 h	"Funny feeling" for about 2 h	"Slightly tipsy" for about 2 h	"Slightly tipsy" for about 2 h	"Slightly tipsy" for about 2 h
Vital signs	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged

M, male; F, female; VAS, visual analog scale; BOL-148, 2-bromo-LSD; IN, intranasal; PO, per os; SC, subcutaneous; h, hours; min, minutes; *Higher doses not tolerated.

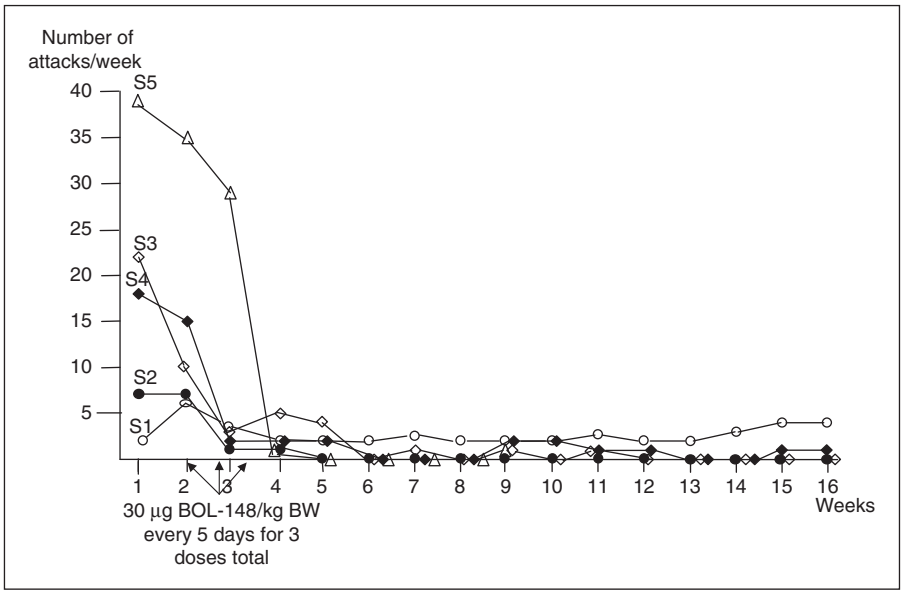

Figure 1. Course of cluster attacks during primary observational period. BOL-148 = 2-bromo-LSD. BW = body weight.

specifically created as a completely non-hallucinogenic form of LSD, but methysergide was developed to have even more potency at serotonin receptors (and less hallucinogenic effects than LSD) (17). While methysergide, an often effective preventative compound if taken on a daily basis for up to six months (18), does not generally induce remissions, the repetitive intravenous and subcutaneous application of 1 mg dihydroergotamine for up to three weeks has been shown in an open retrospective trial to sometimes break a cluster period (19). However, dihydroergotamine is not approved for intravenous or subcutaneous injection in Germany. In addition, BOL-148 seems to exert its effects in a totally different way, as outlined above. Although, after extended and chronic use, both methysergide and dihydroergotamine may be associated with an increased risk for fibrotic complications (such as retroperitoneal fibrosis), this risk is unknown for BOL-148 and seems to be more unlikely from the limited, non-chronic dosing regimen of BOL-148 we employed. Pointedly, there are no pre-clinical studies linking LSD to fibrosis, and, despite an extensive history of illicit use, only one case report is identified in the PubMed database describing prior use of LSD in two individuals with ''idiopathic'' retroperitoneal fibrosis (20). None of the approved ergot-based medications for CH realize the type of profound and lasting treatment response we report from just three oral doses of BOL-148 or in the prior case series of LSD and psilocybin use (7). BOL-148 apparently also differs from methysergide in that prior research indicates methysergide is a less effective preventative for chronic CH than for episodic forms (21).

The results of this case series must be regarded as preliminary, in that they are unblinded and uncontrolled. In acute attack treatment trials, the frequencies of placebo responders were up to 42% while in chronic CH a placebo response as low as 14% was reported in one trial (which employed a very strict endpoint of cessation of attacks), but no placebo response (for efficacy) was noted in five of seven controlled trials (22). Especially since chronic CH patients appear ''to have a relatively modest placebo response'' (22), the extended durability of response to three doses of BOL-148 administered over ten days is unlikely to be an artifact. An additional limitation to this report is that not all known prophylactic alternatives had been tried with our patients to confirm their extent of treatment resistance, but all five subjects did respond to BOL-148. In contrast to the compassionate use setting in this case series, follow-up research with more specific inclusion criteria (e.g. prior verapamil trial of at least 500 mg/day, separation of evaluation of BOL-148 for either episodic or chronic forms) will allow more specific conclusions to be drawn about BOL-148 as a potential treatment for CH. Given that the current standard of care involves interventions that break single headache attacks and reduce pain duration, frequency and intensity of attack cycles, and that identified treatments that extend remission are lacking, the potential breakthrough treatment of BOL-148 warrants wide dissemination of these early findings to encourage aggressive development to randomized controlled trials.

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References

1. May A. Cluster headache: Pathogenesis, diagnosis, and management. *Lancet* 2005; 366: 843–855.
2. International Headache Society. The international classification of headache disorders, 2nd edn. *Cephalalgia* 2004; 24(Suppl 1): 1–160.
3. D'Alessandro R, Gamberini G, Benassi G, Morganti G, Cortelli P, Lugaresi E. Cluster headache in the Republic of San Marino. *Cephalalgia* 1986; 6: 159–162.
4. Leone M, Franzini A, Broggi G, Bussone G. Hypothalamic stimulation for intractable cluster headache: Long-term experience. *Neurology* 2006; 67: 150–152.
5. Bartsch T, Paemeleire K, Goadsby PJ. Neurostimulation approaches to primary headache disorders. *Curr Opin Neurol* 2009; 22(3): 262–268.
6. Schoenen J, Di Clemente L, Vandenheede M, et al. Hypothalamic stimulation in chronic cluster headache: A pilot study of efficacy and mode of action. *Brain* 2005; 128: 940–947.
7. Sewell RA, Halpern JH, Pope HG. Response of cluster headache to psilocybin and LSD. *Neurology* 2006; 66: 1920–1922.
8. Troxler F, Hofmann A. Substitutionen am Ringsystem der Lysergsäure. I—Substitutionen am Indol-Stickstoff. *Helv Chem Acta* 1957; 40(VII): 2160–2170.
9. Bertino JR, Klee GD, Weintraub W. Cholinesterase, d-lysergic acid diethylamide, and 2-bromolysergic acid diethylamide. *J Clin Exp Psychopath* 1959; 20: 218–222.
10. Sicuteri F. Prophylactic treatment of migraine by means of lysergic acid derivatives. *Triangle* 1963; 6(3): 116–125.
11. Clark LD, Bliss EL. Psychopharmacological studies of lysergic acid diethylamide (LSD-25) intoxication; effects of premedication with BOL-128 (2-bromo-d-lysergic acid diethylamide), mescaline, atropine, amobarbital, and chlorpromazine. *AMA Arch Neurol Psychiatry* 1957; 78(6): 653–655.
12. Turner WJ, Almudevar M, Merlis S. Chemotherapeutic trials in psychosis. III. Addendum. 2-brom-d-lysergic acid diethylamide (BOL). *Am J Psychiatry* 1959; 116: 261–262.
13. Koehler PJ, Tfelt-Hansen PC. History of methysergide in migraine. *Cephalalgia* 2008; 28(11): 1126–1135.
14. Frood A. Cluster busters. *Nat Med* 2007; 13(1): 10–11.
15. Balestrieri A, Fontanari D. Acquired and crossed tolerance to mescaline, LSD-25, and BOL-148. *Arch Gen Psychiatry* 1959; 1: 279–282.
16. Passie T, Halpern JH, Stichtenoth DO, Emrich HM, Hintzen A. The pharmacology of lysergic acid diethylamide: A review. *CNS Neurosci Ther* 2008; 14(4): 295–314.
17. Hofmann A. LSD: My problem child. Sarasota, FL, USA: Multidisciplinary Association for Psychedelic Studies, 2005.
18. May A, Leone M, Áfra J, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol* 2006; 13: 1066–1077.
19. Magnoux E, Zlotnik G. Outpatient intravenous dihydroergotamine for refractory cluster headache. *Headache* 2004; 44: 249–255.
20. Aptekar RG, Mitchinson MJ. Retroperitoneal fibrosis in two patients previously exposed to LSD. *Calif Med* 1970; 113: 77–79.
21. Kudrow L. Comparative results of prednisone, methysergide, and lithium therapy in cluster headache. In: Greene R (ed.) *Current concepts in migraine research*. New York: Raven Press, 1978, p.159–163.
22. Nilsson Remahl AI, Laudon Meyer E, Cordonnier C, Goadsby PJ. Placebo response in cluster headache trials: A review. *Cephalalgia* 2003; 23(7): 504–510.

Is BOL-148 hallucinogenic?

Peer Tfelt-Hansen

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Is BOL-148 hallucinogenic?

In a recent paper, Karst et al. describe promising results of the non-hallucinogen 2-bromo-lysergic acid diethylamide (BOL-148) in the prevention of cluster headache in an open study (1). They review the old literature on the lacking hallucinogenic effect of BOL-148 back to 1957 (1). One important reference (2) from 1958 is, however, missing. It is a case study describing how a 28-year-old worker in the laboratory of Harold G. Wolff took BOL-148 0.5 mg for a "pounding" vascular headache. This resulted in a LSD-like delirium for at least seven hours (2). It was published in Annals of Internal Medicine and the reference (2) to it is easily found on PubMed.

Wolff's group concluded, "from these observations it is clear that BOL-148 in relatively small amount produced a delirious reaction similar in almost all respects to that of LSD" (2). This paper should be included in the overall judgement of BOL-148.

References

1. Karst M, Halpern JH, Bernateck M and Passie T. The non-hallucinogen 2-bromo-lysergic acid diethylamine as preventative treatment for cluster headache: a open, non-randomized case series. *Cephalalgia* 2010; 30: 1140–1144.
2. Richards N, Chapman LF, Goodell H and Wolff HG. LSD-like delirium following a small amount of its brom analog (BOL-148). *Ann Intern Med* 1958; 48: 1078–1082.

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Response to Tfelt-Hansen P: Is BOL-148 hallucinogenic?

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Response to Tfelt-Hansen P: Is BOL-148 hallucinogenic?

This is an interesting note about the observation of an altered state of perception and body awareness after ingestion of a single dose of 0.5 mg BOL-148 (1). However, several considerations should be made about the questionable causal relationship of the observed symptoms and the ingestion of BOL-148. It was reported that the young man was "a moderately anxious . . . worker . . . who usually controlled and repressed his affective expressions." Subsequently, we learn that—15 (!) minutes after BOL-148 ingestion—"he complained of lightheadedness and expressed the fear that he might lose consciousness" and "his elevated mood gave way to one of intense anxiety merging into panic."

Everything is told in this: small changes in body awareness had turned into a strong panic attack against the background of an anxious personality increasingly seeking attention for myriad complaints after BOL-148 ingestion, which seems to have been surreptitious ("about 15 minutes later [from ingestion] . . . he sought aid for his state"). Altered and intensified body experiences, such as described in this report, are typical for panic reactions and may be promoted by fixed attention to those bodily reactions to anxiety. Reactions as early as 15 minutes after drug intake also points to anxiety rather than a direct effect of BOL-148: in all published clinical experiments with BOL-148, effects appeared only after a minimum of 30 minutes. Although antipsychotics do not intensify hallucinogenic effects (2,3), this lab worker also complained of a rekindling of peak effects from co-administration of 10 mg of the low-potency neuroleptic chlorpromazine approximately four hours post BOL-148 ingestion. Moreover, it is reasonable to presume that a worker in the laboratory of H.G. Wolff in 1957 *knew* what an altered state looks like after ingestion of an hallucinogenic substance (4), and therefore may have been well-prepared to express certain expectations about the reactions following ingestion of LSD or LSD derivatives. It is not quite clear what, if any, informed consent was offered prior to drug administration, and it also appears that this lab worker may have self-administered BOL-148 without permission, as noted above. No information is mentioned about the source of the BOL-148, its purity and chemical composition, and so on. Finally, no evidence of the major typical effects of LSD—such as pseudo-hallucinations, intensification of visual imagery with eyes closed, synesthesias, or distortions of time and space—was given in this case report (5). The altered state described cannot be characterized as a "toxic delirium" because it was reported that the subject was always completely oriented to time, space, situation and person, and had no consistent clouding of consciousness and no hallucinations.

In contrast, there are numerous reports describing no typical LSD-like alterations from BOL-148 at doses comparable to that in this single case report, such as our study (6), and at much larger doses (2,7–11). The overall consistency of research reports on the mild subjective effects of BOL-148 is why this drug is currently referred to as the "non-hallucinogen BOL" (5). We therefore conclude that the single case report mentioned was not worthy of discussion in our original report, but we are grateful to have this opportunity to provide reassuring clarification for what remains a quite promising new approach for the treatment of cluster headache.

References

1. Richards N, Chapman LF, Goodell H and Wolff HG. LSD-like delirium following ingestion of a small amount of its brom analog (BOL-148). *Ann Intern Med* 1958; 48(5): 1078–1082.
2. Nichols DE. Hallucinogens. *Pharmacol Ther* 2004; 101(2): 131–181.
3. Rasmussen K and Aghajanian GK. Potency of antipsychotics in reversing the effects of a hallucinogenic drug on locus coeruleus neurons correlates with 5-HT2 binding affinity. *Neuropsychopharmacol* 1988; 1(2): 101–107.
4. Berlin L, Guthrie T, Wieder A, Goodell H and Wolff HG. Studies in human cerebral function: the effects of

mescaline and lysergic acid on cerebral processes pertinent to creative activity. *J Nerv Ment Dis* 1955; 122(5): 487–491.
5. Hintzen A and Passie T. *The pharmacology of LSD*. Oxford: Oxford University Press, 2010.
6. Karst M, Halpern JH, Bernateck M and Passie T. The non-hallucinogenic 2-bromo-lysergic acid diethylamide as preventive treatment for cluster headache: an open, non-randomized case series. *Cephalalgia* 2010; 30(9): 1140–1144.
7. Hirsch MW, Jarvik ME and Abramson HA. Lysergic acid diethylamide (LSD-25). XVIII. Effects of LSD-25 and six related drugs upon handwriting. *J Psychol* 1956; 41: 11–22.
8. Rothlin E. Pharmacology of lysergic acid diethylamide (LSD) and some of its related compounds. *J Pharm Pharmacol* 1957; 9(9): 569–587.
9. Bertino JR, Klee GD and Weintraub W. Cholinesterase, d-lysergic acid diethylamide, and 2-bromolysergic acid diethylamide. *J Clin Exp Psychopath* 1959; 20: 218–222.
10. Isbell H, Miner EJ and Logan CR. Relationships of psychotomimetic to anti-serotonin potencies of congeners of lyergic acid diethylamide (LSD-25). *Psychopharmacol (Berl)* 1959; 1(1): 20–28.
11. Jacobs BL. *Hallucinogens: Neurochemical, behavioral, and clinical perspectives*. New York: Raven Press, 1984.

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