Evaluation of LY573144 (lasmiditan) in a preclinical model of medication overuse headache

Jill C Rau[1], Edita Navratilova[2] , Janice Oyarzo[1], Kirk W Johnson[3], Sheena K Aurora[3], Todd J Schwedt[1], David W Dodick[1] and Frank Porreca[1,2]

Abstract

Background: Medication overuse is a significant issue that complicates the treatment of headache disorders. The most effective medications for the acute treatment of migraine all have the capacity to induce medication overuse headache (MOH). Novel acute migraine-specific treatments are being developed. However, because the mechanism(s) underlying medication overuse headache are not well understood, it is difficult to predict whether any particular acute medication will induce MOH in susceptible individuals. LY573144 (lasmiditan), a 5-HT$_{1F}$ receptor agonist, has recently been shown to be effective in the acute treatment of migraine in phase 3 trials. The aim of this study is to determine whether frequent administration of lasmiditan induces behaviors consistent with MOH in a pre-clinical rat model.

Methods: Sprague Dawley rats were administered six doses of lasmiditan (10 mg/kg), sumatriptan (10 mg/kg), or sterile water orally over 2 weeks and cutaneous allodynia was evaluated regularly in the periorbital and hindpaw regions using von Frey filaments. Testing continued until mechanosensitivity returned to baseline levels. Rats were then submitted to bright light stress (BLS) or nitric oxide (NO) donor administration and were again evaluated for cutaneous allodynia in the periorbital and hindpaw regions hourly for 5 hours.

Results: Both lasmiditan and sumatriptan exhibited comparable levels of drug-induced cutaneous allodynia in both the periorbital and hindpaw regions, which resolved after cessation of drug administration. Both lasmiditan and sumatriptan pre-treatment resulted in cutaneous allodynia that was evoked by either BLS or NO donor.

Conclusions: In a pre-clinical rat model of MOH, oral lasmiditan, like sumatriptan, induced acute transient cutaneous allodynia in the periorbital and hindpaw regions that after resolution could be re-evoked by putative migraine triggers. These results suggest that lasmiditan has the capacity to induce MOH through persistent latent peripheral and central sensitization mechanisms.

Keywords
Pain, migraine, allodynia, stress, lasmiditan, sumatriptan

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Introduction

Frequent use of acute headache medications or medication overuse in individuals with headache disorders can lead to medication overuse headache (MOH). MOH is characterized by an increased frequency of headache attacks and disability (1–3). MOH is defined by the International Classification of Headache Disorders 3rd edition (ICHD-3) as a headache that develops as a consequence of regular overuse of symptomatic headache medication in a person with a

[1]Mayo Clinic, Scottsdale, AZ, USA
[2]Department of Pharmacology, Arizona Health Sciences Center, University of Arizona, Tucson, AZ, USA
[3]Eli Lilly, Indianapolis, IN, USA

Corresponding author:
Frank Porreca, Department of Pharmacology, University of Arizona, Tucson, AZ 85724, USA.
Email: frankp@medadmin.arizona.edu

pre-existing headache disorder and that occurs on more than 14 days per month for more than 3 months and cannot be better accounted for by another ICHD-3 diagnosis (4). It is estimated that the prevalence of MOH is 1–2% in the general population (5–10), affecting over 100 million people worldwide (11). MOH comes at a significant cost to the individual and society, both financially (12–15) and psychosocially (6,16). MOH has been estimated by the World Health Organization's Global Burden of Disease Study 2017 as being responsible for over 9.5 million years lived with disability, more than any other neurologic disorder excluding other headache disorders (11).

The majority of drug classes used to treat acute headache, including opioids, barbiturate containing medications, ergotamines, triptans, and simple analgesics such as non-steroidal anti-inflammatories (NSAIDs) and acetaminophen/paracetamol, have been implicated in MOH (2,3,17,18). In individuals with migraine, medication overuse is a risk factor for the transformation of episodic to chronic migraine (2) which is associated with increased disability and decreased quality of life (19–21). It has been estimated that migraine accounts for up to 67–100% of the primary headache types of those with MOH (22–24). Triptans, 5-HT$_{1B/1D}$ agonists, specifically designed for the acute treatment of migraine and perhaps the most effective migraine abortive medications, are associated with MOH in 5–18% of patients (22,25,26).

The need for new acute headache medications that do not worsen the underlying headache condition is widely recognized by headache providers and patients with headache disorders. However, there is incomplete understanding of the mechanism by which each of these medications could induce worsening of the headache condition, and therefore it is somewhat unpredictable as to whether new medications designed to acutely treat migraine attacks will induce MOH (27).

Recently, a new class of migraine medications, 5-HT$_{1F}$ receptor agonists (the ditans), has been developed for the acute treatment of migraine. Lasmiditan is a 5-HT$_{1F}$ receptor agonist that has been demonstrated to be effective for the acute treatment of migraine (28,29) and has recently been FDA approved.

The main goal of this study is to determine if lasmiditan, a 5-HT$_{1F}$ agonist, produces MOH similar to sumatriptan, a 5-HT$_{1B/1D}$ agonist (30), in a preclinical model. Cutaneous allodynia and in particular, facial or periorbital cutaneous allodynia, is often used as a surrogate for headache in animal models (31–33). Thermal and mechanical cutaneous hypersensitivity are seen in patients with migraine (34,35) and medication overuse headache (2,36). Cutaneous allodynia usually occurs during headache attacks (ictally) but may persist between attacks (interictally) in patients with chronic

migraine (CM) (37) and has higher prevalence in patients with CM compared to episodic migraine (EM) (2). We previously published a rodent model of MOH using sustained systemic administration of sumatriptan or morphine (38). Here we use a similar model using the oral administration of sumatriptan or lasmiditan.

Materials and methods

Animals

Adult male Sprague Dawley (SD) rats (Harlan Laboratories Inc., Indianapolis, IN, USA), initially weighing 175–225 g, were maintained three per cage in a climate-controlled room at $22 \pm 2°C$ on a 14-hour light/10-hour dark cycle (lights on at 5 am and off at 7 pm) with free access to food and water. Studies were conducted during the animals' light cycle following approval by the Institutional Animal Care and Use Committee of Mayo Clinic Arizona.

Drugs

Lasmiditan/LY573144 (Eli Lilly, Indianapolis, IN, USA), sumatriptan succinate (Abmole Bioscience, Houston, TX, USA) and sodium nitroprusside (SNP; Sigma-Aldrich, St. Loius, MO, USA) were dissolved in distilled water.

Dosing

Six doses of sumatriptan, lasmiditan or vehicle (distilled water), were administered over 2 weeks by oral gavage at a volume of 3 ml/kg. Sumatriptan was administered at 6 mg/kg or 10 mg/kg. Lasmiditan was administered at 10 mg/kg.

Pain measurement

Mechanical periorbital and hindpaw allodynia was measured using calibrated von Frey monofilaments prior to the first priming drug treatment (i.e. baseline), in the mornings before each additional drug dosing and then intermittently after drug discontinuation over a 21-day time course. In Experiments 2 and 3, von Frey testing was omitted on dosing days 3 and 6, respectively, due to unforeseen scheduling conflicts for the technician. In the von Frey tests, the mechanical stimulations were incrementally increased until a positive response was obtained, and then decreased until a negative result was observed. This was repeated until three changes in behavior were determined ("up and down" method) (39). The 50% paw withdrawal threshold was determined as $(10^{[Xf+k\delta]})/10,000$, where Xf = the value of the last von Frey filament employed, k = Dixon value for the positive/negative pattern, and

δ = the logarithmic difference between stimuli. The cutoff values for rats were no less than 0.2 g and no higher than 15 g (5.18 filament).

Putative migraine triggers

Bright light stress (BLS). Unrestrained rats were exposed to bright light (1000 lumens) for 1 h each on two consecutive days (days 21 and 22, or as indicated) when mechanical thresholds had returned to basal levels. Our previous investigations demonstrate significant BLS-induced allodynia after the first BLS exposure, but even more robust allodynia after the second BLS episode (40). Therefore, in this study, we evaluated mechanical periorbital and hindpaw allodynia only after the second BLS on day 22 with hourly measurements over a 5 h time course.

Nitric oxide (NO) donor. After resolution of drug-induced allodynia and stress-induced allodynia (on day 28 or 33), rats were administered an NO donor (sodium nitroprusside). Sodium nitroprusside was dissolved in saline at 3 mg/ml and administered i.p. to the rats based on their weight at 3 mg/kg. Mechanical facial and hindpaw allodynia was measured over a 5 h time course post NO donor.

General experimental design overview

Does repeated oral administration of sumatriptan induce cephalic and extracephalic pain dose dependently? Twenty-six male SD rats were divided into three groups based on drug treatment (Group 1: sumatriptan 6 mg/kg, p.o.; n = 9; Group 2: sumatriptan 10 mg/kg, p.o.; n = 9; Group 3: water, p.o; n = 8). Rats were administered the assigned drug treatment on days 0, 2, 5, 7, 8, and 9 (total of six doses). Periorbital and hindpaw withdrawal responses before (baseline) and periodically over 22 days after drug treatment were assessed to measure allodynia. Rats were then exposed to stress (bright lights for 1 h) on days 22 and 23, and periorbital and hindpaw allodynia was assessed on day 23 hourly for 5 h following BLS. On day 33, rats were exposed to NO donor, and periorbital and hindpaw allodynia was assessed at 1–5 h time points.

Does oral sumatriptan, but not lasmiditan, promote stress-induced cephalic and extracephalic pain? Three sets of experiments comparing sumatriptan and lasmiditan-induced allodynia were performed:

Experiment 1: Twenty-four male SD rats were divided into three groups based on drug treatment (Group 1: sumatriptan 10 mg/kg, p.o.; n = 6; Group 2: lasmiditan 10 mg/kg, p.o.; n = 12; Group 3: water; n = 6). Rats were administered the assigned drug treatment on days 0, 2, 4, 7, 10 and 11. Periorbital and hindpaw

withdrawal responses before (baseline) and periodically over 21 days after drug treatment were assessed to measure allodynia. Rats were then exposed to stress (bright lights for 1 h) on days 21 and 22, and periorbital and hindpaw allodynia was assessed on day 22 at 1–5 h time points. On day 28, rats were exposed to NO donor, and periorbital and hindpaw allodynia was assessed at 1–5 h time points.

Experiment 2: Twenty-four male SD rats were divided into three treatment groups (Group 1: sumatriptan 10 mg/kg, p.o.; n = 6; Group 2: lasmiditan 10 mg/kg, p.o.; n = 12; Group 3: water; n = 6). Rats were administered the assigned drug treatment on days 0, 3, 4, 7, 9 and 11. Periorbital and hindpaw withdrawal responses before (baseline) and periodically over 21 days after drug treatment were assessed to measure allodynia.

Experiment 3: Twenty-four male SD rats were divided into three groups based on drug treatment (Group 1: sumatriptan 10 mg/kg, p.o.; n = 9; Group 2: lasmiditan 10 mg/kg, p.o.; n = 9; Group 3: water; n = 6). Rats were administered the assigned drug treatment on days 0, 5, 6, 8, 12 and 13. Periorbital and hindpaw withdrawal responses before (baseline) and periodically over 21 days after drug treatment were assessed to measure allodynia. Rats were then exposed to BLS for 1 h on day 21, and periorbital and hindpaw allodynia was assessed at 1–5 h time points.

Data analysis

GraphPad Prism 7 (GraphPad Software, La Jolla, CA, USA) was used for statistical data analysis. Two-way repeated measures ANOVA, with time as a within-subject factor and treatment as a between-subject factor, followed by Tukey's *post hoc* multiple-comparisons test, was performed to analyze significant differences between treatment groups within one experiment. Two-way ANOVA with Tukey's multiple comparisons test was used to assess between-group differences in combined multiple experiment data analysis. Statistical significance was set at $p < 0.05$. All data were presented as mean $\pm$ SEM.

Results

Repeated oral administration of sumatriptan promotes transient allodynia and long-lasting sensitization revealed as stress-induced allodynia and NO donor-induced allodynia

Repeated oral administration of sumatriptan (6 mg/kg or 10 mg/kg, six doses) promoted transient hindpaw and periorbital allodynia that resolved by day 14 (Figure 1(a) and (b), Table 1). In sumatriptan-primed rats, two episodes of bright

light stress on days 22 and 23 induced hindpaw and periorbital allodynia lasting 3–4 h with full recovery at 5 h after BLS (Figure 1(c) and (d), Table 1). In the same animals, sodium nitroprusside, a NO donor, administered on day 33 elicited hindpaw and periorbital allodynia (Figure 1(e) and (f), Table 1). The results demonstrate long-lasting sensitization following sumatriptan priming. Sumatriptan at 6 and 10 mg/kg doses elicited both acute and provoked tactile allodynia. The effects of the higher dose were consistently larger in all graphs and reached significance at several time points. For that reason, the 10 mg/kg dose was chosen for further studies.

Repeated oral administration of lasmiditan promotes transient allodynia and long-lasting sensitization revealed as stress-induced allodynia and NO donor-induced allodynia that were indistinguishable from allodynia observed in sumatriptan-primed rats

Sumatriptan and lasmiditan are available clinically at similar oral doses of 25, 50 or 100 mg (sumatriptan) and 50 and 100 mg (lasmiditan). We evaluated whether the same doses of lasmiditan and sumatriptan produce similar levels of MOH. Repeated oral administration of

lasmiditan (10 mg/kg, six doses) promoted transient hindpaw and periorbital allodynia, similar to sumatriptan-induced allodynia, that resolved by day 21 (Figure 2(a) and (b), Table 1). In lasmiditan-primed rats, two episodes of BLS on days 21 and 22 induced hindpaw and periorbital allodynia lasting 4–5 h that was statistically indistinguishable from stress-induced allodynia in sumatriptan-primed rats (Figure 2(c) and (d), Table 1). In the same animals, sodium nitroprusside, a NO donor, administered on day 28 elicited allodynia, demonstrating long lasting sensitization following priming with lasmiditan or sumatriptan (Figure 2(e) and (f), Table 1).

This experiment was repeated three times with slightly different dosing regiments (Figures 3 and 4, Table 1) and showed the same overall results. Average sumatriptan- and lasmiditan- induced allodynia observed in all three experiments was plotted as a function of number of repeated doses (Figure 5, Table 1) and showed no difference between sumatriptan and lasmiditan. In addition, these data suggest that the variations in dosing times likely do not affect the priming. Instead, priming appears to be induced cumulatively over time by each additional dose. Note that on dosing days, von Frey testing
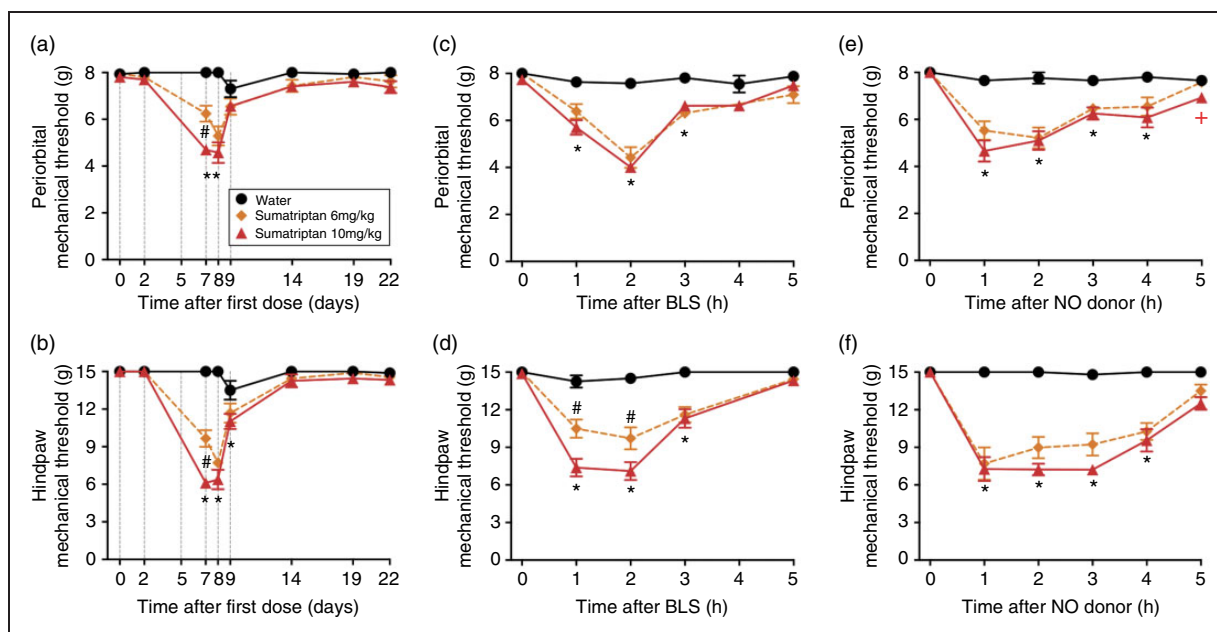

Figure 1. Repeated oral administration of sumatriptan elicits acute tactile periorbital and hindpaw allodynia and sensitizes the animals to putative migraine triggers. Sumatriptan (6 mg/kg or 10 mg/kg) or water were given PO on days 0, 2, 5, 7, 8, and 9 (grey dotted lines). Mechanical periorbital (a) and hindpaw (b) allodynia were measured at baseline (0) and on indicated days following the first treatment dose over a time course of 22 days. Two episodes of bright light stress (BLS) on days 22 and 23 reinstated periorbital (c) and hindpaw (d) allodynia only in sumatriptan-primed rats. In the same animals, subsequent NO donor on day 33 reinstated periorbital (e) and hindpaw (f) allodynia only in sumatriptan-primed rats. A two-way ANOVA with Tukey's multiple comparison test shows significant difference between water- and sumatriptan-treated rats at indicated times: Asterisk (*) indicates that both sumatriptan doses are significantly different from water, red plus sign (+) indicates that only the 10 mg/kg sumatriptan dose is significantly different, (#) indicates a significant difference between the 6 mg/kg and 10 mg/kg doses. Data are plotted as means ± SEM, n = 8–9.

Table 1. Summary of statistical analyses. p values and F ratios for statistical analyses used in Figures 1–5.

Figure	Analysis	Time	Treatment	Interaction
1(a)	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	RM ANOVA	$F_{(8, 184)} = 35.4$	$F_{(2, 23)} = 62.3$	$F_{(16, 184)} = 9.56$
1(b)	2-way	$p < 0.001$	$p < 0.0001$	$p < 0001$
	RM ANOVA	$F_{(8, 184)} = 103$	$F_{(2, 23)} = 90.2$	$F_{(8, 184)} = 25.9$
1©	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	RM ANOVA	$F_{(4, 92)} = 62.8$	$F_{(2, 23)} = 36.1$	$F_{(8, 92)} = 11.8$
1(d)	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	RM ANOVA	$F_{(4, 92)} = 54.8$	$F_{(2, 23)} = 44.8$	$F_{(8, 92)} = 12.1$
1(e)	2-way	$p < 0.0001$	$p < 0.0001$	$p = 0.0002$
	RM ANOVA	$F_{(5, 75)} = 19.8$	$F_{(2, 15)} = 63.3$	$F_{(10, 75)} = 4.12$
1(f)	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	RM ANOVA	$F_{(5, 75)} = 29.2$	$F_{(2, 15)} = 174$	$F_{(10, 75)} = 7.01$
2(a)	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	RM ANOVA	$F_{(7, 147)} = 14.3$	$F_{(2, 21)} = 53.3$	$F_{(14, 147)} = 3.88$
2(b)	2-way	$p < 0.001$	$p < 0.0001$	$p < 0001$
	RM ANOVA	$F_{(7, 147)} = 32.7$	$F_{(2, 21)} = 62.3$	$F_{(14, 147)} = 7.76$
2(c)	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0184$
	RM ANOVA	$F_{(5, 105)} = 14.6$	$F_{(2, 21)} = 17.8$	$F_{(10, 105)} = 2.28$
2(d)	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	RM ANOVA	$F_{(5, 105)} = 22.5$	$F_{(2, 21)} = 45.0$	$F_{(10, 105)} = 4.24$
2(e)	2-way	$p < 0.0001$	$p < 0.0001$	$p = 0.1274$
	RM ANOVA	$F_{(5, 105)} = 10.9$	$F_{(2, 21)} = 54.4$	$F_{(10, 105)} = 1.57$
2(f)	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	RM ANOVA	$F_{(5, 105)} = 21.2$	$F_{(2, 21)} = 32.2$	$F_{(10, 105)} = 4.78$
3(a)	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	RM ANOVA	$F_{(7, 147)} = 20.1$	$F_{(2, 21)} = 102$	$F_{(14, 147)} = 4.84$
3(b)	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	RM ANOVA	$F_{(7, 147)} = 44.4$	$F_{(2, 21)} = 81.2$	$F_{(14, 147)} = 11.3$
4(a)	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	RM ANOVA	$F_{(6, 126)} = 28.5$	$F_{(2, 21)} = 63.1$	$F_{(12, 126)} = 7.06$
4(b)	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	RM ANOVA	$F_{(6, 126)} = 39.6$	$F_{(2, 21)} = 47.3$	$F_{(12, 126)} = 9.75$
4(c)	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0233$
	RM ANOVA	$F_{(3, 63)} = 19.8$	$F_{(2, 21)} = 47.4$	$F_{(6, 63)} = 2.66$
4(d)	2-way	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	RM ANOVA	$F_{(3, 63)} = 26.2$	$F_{(2, 21)} = 40.4$	$F_{(6, 63)} = 5.78$
5(a)	2-way ANOVA	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
		$F_{(8, 525)} = 36.7$	$F_{(2, 525)} = 106$	$F_{(16, 525)} = 8.44$
5(b)	2-way ANOVA	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
		$F_{(8, 525)} = 64.3$	$F_{(2, 525)} = 124$	$F_{(16, 525)} = 13.8$

was performed before drug administration, eliminating any possible acute effects of drug concentration in the circulation.

Discussion

This study demonstrated that equivalent doses of sumatriptan (10 mg/kg) and lasmiditan (10 mg/kg) administered repeatedly to rats via the oral route elicited comparable levels and time course of tactile periorbital and hindpaw allodynia. Additionally, after resolution of drug-induced transient allodynia, both sumatriptan-primed and lasmiditan-primed rats were susceptible to bright light stress-induced, or NO donor-induced allodynia, demonstrating long-lasting central and peripheral sensitization. This is similar to the allodynia or increased sensitization induced in patients with primary headache disorders that is associated with frequent use of acute medications or MOH.

The pathophysiology of MOH is not fully understood. The majority of patients with medication overuse have migraine as an underlying primary headache. Imaging studies, however, indicate differences in the brains of patients with migraine and with MOH, including reductions in the grey matter volume in areas associated with pain processing (41,42), and functional reactivity and resting state connectivity of brain regions involved in pain processing and modulation as
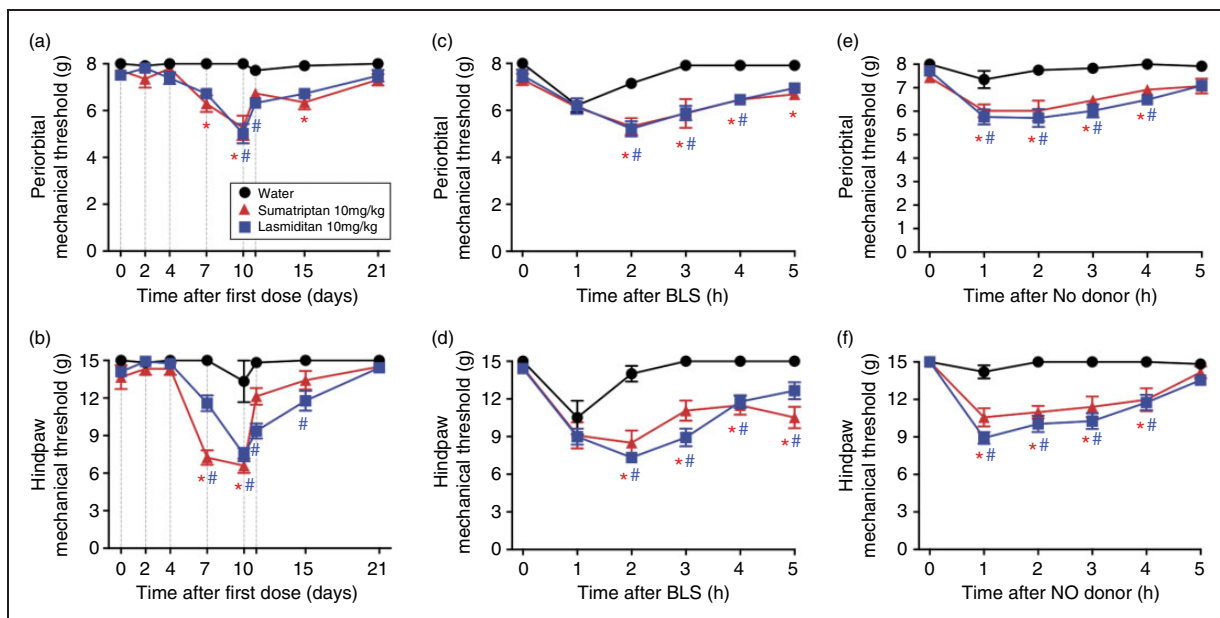
Figure 2. Repeated oral administration of lasmiditan elicits acute tactile periorbital and hindpaw allodynia and sensitizes the animals to putative migraine triggers (Experiment 1). Lasmiditan (10 mg/kg), sumatriptan (10 mg/kg) or water were given PO on days 0, 2, 4, 7, 10, and 11 (dotted lines). Mechanical periorbital (a) and hindpaw (b) allodynia were measured at baseline (0) and on indicated days following the first treatment dose over a time course of 21 days. Two episodes of bright light stress on days 21 and 22 reinstated periorbital (c) and hindpaw (d) allodynia in both lasmiditan and sumatriptan-primed rats. Subsequent NO donor administration on day 28 reinstated periorbital (e) and hindpaw (f) allodynia only in rats primed with lasmiditan or sumatriptan. A two-way ANOVA with Tukey's multiple comparison test shows significant difference at indicated times between water and sumatriptan-treated rats (asterisk; *) and between water and lasmiditan (hashtag; #). Data are plotted as mean ± SEM, n = 6–12.
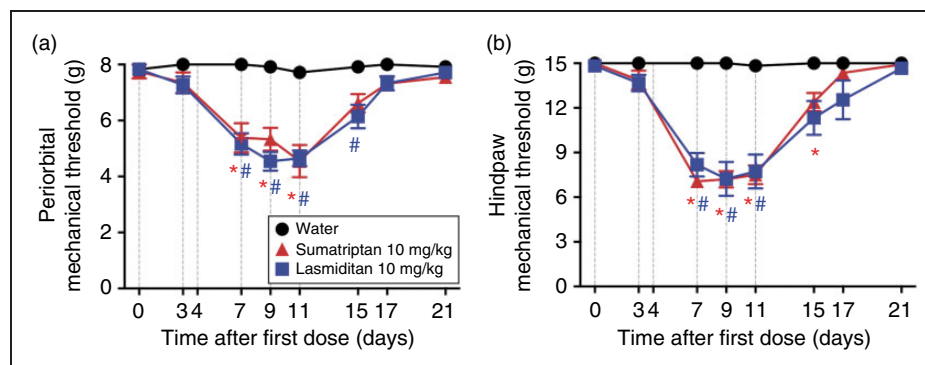

Figure 3. Repeated oral administration of lasmiditan elicits acute tactile periorbital and hindpaw allodynia (Experiment 2). Lasmiditan (10 mg/kg), sumatriptan (10 mg/kg) or water were given PO on days 0, 3, 4, 7, 9, and 11 (dotted lines). Mechanical periorbital (a) and hindpaw (b) allodynia were measured at baseline (0) and periodically over a time course of 21 days following the first treatment dose. A two-way ANOVA with Tukey's multiple comparison test shows significant difference at indicated times between water and sumatriptan-treated rats (asterisk; *) and between water and lasmiditan (hashtag; #). Data are plotted as mean ± SEM, n = 6–12.

well as cognitive and affective processing of pain (43). Furthermore, genetic studies have suggested particular gene polymorphisms may increase the risk of patients developing MOH, including genes involved in dopaminergic and serotonergic pathways (44). These studies augment findings that the serotonin (5-HT) system is altered in MOH, with decreased 5-HT levels (45) and increased levels of 5-HT receptors (46) in patients with MOH. Similar changes in the 5-HT system were seen in rats administered frequent repeated doses of simple analgesic (47). Neural adaptations, possibly including the 5-HT system, are thought to induce a state of latent sensitization and may represent a pathophysiological mechanism that accounts for MOH and the progression from episodic to chronic migraine (30).
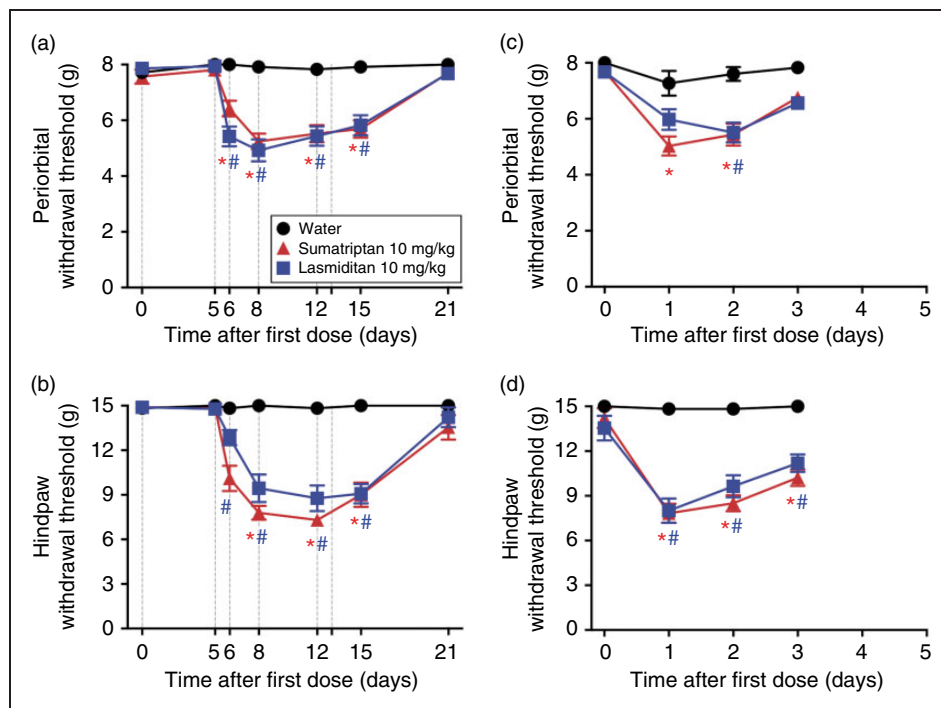
Figure 4. Repeated oral administration of lasmiditan elicits acute tactile periorbital and hindpaw allodynia and sensitizes the animals to stress (Experiment 3). Lasmiditan (10 mg/kg), sumatriptan (10 mg/kg) or water were given PO on days 0, 5, 6, 8, 12, and 13 (dotted lines). Mechanical periorbital (a) and hindpaw (b) allodynia were measured at baseline (0) and on indicated days following the first treatment dose over a time course of 21 days. Two episodes of bright light stress on days 20 and 21 reinstated periorbital (c) and hindpaw (d) allodynia in both lasmiditan and sumatriptan-primed rats. A two-way ANOVA with Tukey's multiple comparison test shows significant difference at indicated times between water and sumatriptan-treated rats (asterisk; *) and between water and lasmiditan (hashtag; #). Data are plotted as mean ± SEM, n = 6–12.
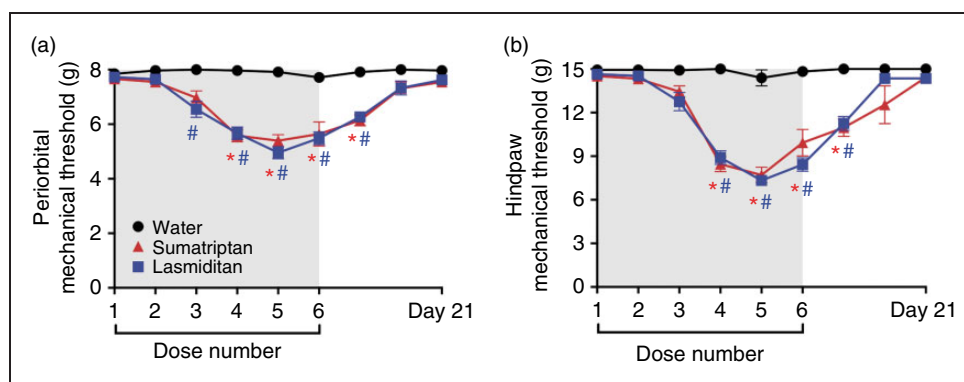

Figure 5. Periorbital and hindpaw allodynia in lasmiditan (10 mg/kg) or sumatriptan (10 mg/kg) primed rats (Experiments 1–3). Combined withdrawal threshold data from Experiments 1–3 are plotted as a function of dose number. Six oral doses of either water, sumatriptan or lasmiditan were administered on days: 0 (dose 1); 2, 3 or 5 (dose 2); 4, 4 or 6 (dose 3); 7, 7 or 8 (dose 4); 10, 9 or 12 (dose 5) and 11, 11 or 13 (dose 6). In all experiments, repeated lasmiditan or sumatripan administration elicited periorbital (a) and hindpaw (b) allodynia, allowing for establishment of a more accurate time course as a function of number of repeated drug doses. Both periorbital and hindpaw allodynia started after two or three doses and was still observed on 2–4 days after the last dose (day 13–15) but resolved by day 21. A two-way ANOVA with Tukey's *post hoc* test shows significant difference between water and sumatriptan-treated rats (asterisk; *) and between water and lasmiditan (hashtag; #). Data are plotted as mean ± SEM, n = 18 (water), 21 (sumatriptan), and 33 (lasmiditan).

Lasmiditan is a highly-specific 5-HT$_{1F}$ receptor agonist developed for the purpose of aborting migraine attacks through the activation of neural 5-HT$_{1F}$ receptors on trigeminal fibers and subsequently inhibiting trigeminal CGRP release, while avoiding the vasoconstrictive effect of the triptans by having minimal affinity for 5-HT$_{1B}$ receptors in the vasculature (48–50). The administration of lasmiditan has been shown to reduce potassium chloride-induced CGRP release from the dura mater, trigeminal ganglion and trigeminal nucleus caudalis of mice (51). It has been suggested that lasmiditan may also have an effect on central descending antinociceptive pathways (52). The efficacy and safety of lasmiditan for the termination of migraine attacks have been demonstrated in Phase 3 clinical trials, which have included patients with cardiovascular risk factors (28,29,53). Thus, lasmiditan may fill a need for an additional, highly effective acute migraine medication that can be used in patients with cardiovascular risk factors.

While there is hope that the new acutely acting migraine-specific medications to terminate migraine, such as lasmiditan, will not cause MOH (54), this rodent model suggests that lasmiditan may have the same capacity as triptans to cause MOH when used with high frequency. However, the precise predictive validity of this rodent model cannot be determined at present primarily due to the absence of an acute pharmacotherapy for migraine that has not been linked to clinical MOH to function as a negative control. An additional limitation of this study is that the animal model assessed allodynia induced by external stressors rather than measuring an increased frequency of headache as associated with clinical MOH. The predictive value of preclinical models remains uncertain and, for this reason, the propensity for lasmiditan to induce MOH will ultimately be assessed clinically.

A limitation of this study is that it was performed with exclusively male rats. Gender differences in risk of MOH and in cutaneous allodynia have been identified in humans. In a US nationwide online study, allodynia was reported in a higher percentage of women with migraine than in men with migraine (55). Furthermore, previous studies have shown women to be at higher risk for MOH than men (7). However, recently Schwedt et al. (36), in a large national survey of US adults with migraine, found that cutaneous allodynia was associated with acute medication overuse in male respondents with migraine but not in female respondents. The effects of sex on cutaneous allodynia are not clear from human epidemiologic studies and thus it would be interesting to observe if sex differences existed in this rodent model of MOH.

Conclusions

This study demonstrates that repeated oral administration of 10 mg/kg dose of lasmiditan promotes transient cephalic and hindpaw allodynia that resolves following discontinuation of the drug. At time points when sensory thresholds are at baseline levels, stress or NO donor reinstates cephalic and hindpaw allodynia, revealing a drug induced "latent sensitization". The results are similar to sumatriptan. The development of allodynia and increase in sensitivity to putative migraine triggers is interpreted as a preclinical measure of vulnerability to medication overuse headache.

Key findings

- In male Sprague Dawley rats, the frequent oral administration of either lasmiditan or sumatriptan elicited significant cutaneous allodynia, both periorbitally and in the hindpaw, that resolved after cessation of medication administration.
- After its initial resolution, cutaneous allodynia could be re-evoked in both the periorbital and hindpaw regions by putative migraine triggers, including exposure to bright light stress and administration of a nitric oxide donor substance.
- In this pre-clinical model of MOH, frequent consumption of lasmiditan, like sumatriptan, induces both transient cutaneous allodynia representative of heightened pain sensitivity in the MOH state as well as persistent latent central and peripheral sensitization demonstrated by susceptibility to putative migraine triggers.
- This study suggests that, like the triptans, lasmiditan could potentially induce MOH.

ORCID iD

Edita Navratilova https://orcid.org/0000-0002-1497-125X

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