▪ Headache Medicine 2024, 15(3): 145-150 ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

▪ DOI: 10.48208/HeadacheMed.2024.30

Original

The influence between migraine preven drugs and sumatriptan succinate on motor activity

Edison Matos Novak[1,2], Pedro André Kowacs[1], Guilherme Armando de Carvalho[1,2], Mariane Christina Savio[1,2], Lucas Pires Augusto[1,2], Conrado Regis Borges[1,2], Gustavo Ribas[1,2], Giovana Costa Guinski[1,2], Sandra Monarin[1,2], Marco Antonio Takashi Utiumi[3], Élcio Juliato Piovesan[1,2]

[1]Headache Unit, Neurology Division, Internal Medicine Department, Hospital of Clinical / Federal University of Parana (HC/UFPR), Curitiba, Parana, Brazil
[2]Health Science Experimental Laboratory Federal University of Parana, Curitiba, Parana, Brazil
[3]Headache Center at the Sao Jose Neurology Clinic, Curitiba, Parana, Brazil

Élcio Juliato Piovesan
piovesan1@hotmail.com

Edited by:
Marcelo Moraes Valença

Background and aim
The motor effect of sumatriptan succinate (SS) and whether or not it is associated with different classes of migraine preventive drugs has yet to be studied. We aimed to analyze such drugs' influence on animal motor activity, verifying their effect when used alone or in combination.

Methods
Male Norvegicus rats (n=98) were treated with routinely prescribed migraine preventive drugs and divided into five groups: isotonic saline solution (ISS, control), propranolol, topiramate, flunarizine, and amitriptyline. After five days of daily treatment, the animals received acute treatment with either ISS or Sumatriptan succinate (SS). The drug's influence on motor function behavior was assessed with the rotarod and open field tests.

Results
Propranolol and flunarizine interfered with the motor activity (p=0.006 and 0.002, respectively). SS did not cause motor changes when administered alone. However the SS combined with amitriptyline increased the number of rearings (p=0,045) and reduced the immobility time (p=0.041).

Conclusions
SS exerted no motor effect, although flunarizine and propranolol could produced motor interference.

Keywords:
motor influence
migraine
prophylactic treatment
sumatriptan

Submited: January 8, 2024
Accepted: August 3, 2024
Published online: September 30, 2024

Introduction

Migraine is one of the most prevalent neurological diseases in humankind, occurring in approximately 17% of women and 6% of adult men (1). The migraine treatment can be acute or preventive (prophylactic), and subjects with frequent and severe attacks usually need both. The preventive treatment acts on the headache's physiopathological genesis, significantly reducing its intensity, frequency, and duration and increasing the effect of the drugs used in the acute treatment (2,3). The adequate control of migraine reduces direct and indirect costs, interferes with the intensity of the comorbidities, and prevents future cardiovascular complications, thus providing a better quality of the migraineur's life.

One of the most used drugs for acute management is sumatriptan succinate (SS), a selective 5-hydroxytryptamine receptor (5HT1B-1D) agonist (2). For the prophylactic treatment, the pharmacological classes most commonly used are beta-blockers (propranolol and metoprolol), neuromodulators (divalproex sodium, topiramate, and gabapentin), calcium channel blockers (flunarizine), tricyclic antidepressants (amitriptyline) and mitochondrial metabolic modulators (coenzyme Q10 and riboflavin) among others (3).

This medical disorder impairs patients' behavior and performance abilities, increasing the risk of errors that can lead to vehicle crashes and domestic and professional accidents. Those accidents can be caused by impairments of attention or perception (vision, hearing, somatosensory, and vestibular inputs), response selection and implementation, emotional state, level of arousal or sleepiness, psychomotor factors, general mobility, and awareness of the situation and itself (metacognition) (4). Within these concepts, migraine can impact the ability to drive, work, or carry out social and domestic activities during any of its phases: premonitory, aura, headache, and recovery. Currently, we know very little about the influence of prophylactic drugs and those used for the acute treatment of migraine within these various domains of metacognition.

Regarding the psychomotor domain, many of these drugs can produce various adverse effects (e.g., beta-blockers and calcium channel blockers) (5,6). The clinical motor effect of sumatriptan and whether or not it is associated with various classes of prophylactic drugs have not been studied yet. The primary objective of this study was to analyze the influence of such drugs on animal on motor activity. The secondary objective was to verify these drugs' effects when used alone or in combination – a frequent scenario in clinical practice.

Methods

Animals: Experiments were conducted on 98 male Norvegicus Wistar rats weighing 160-190 g (mean=175 g). The animals were housed four by four in a cage at 22±1°C with a 12-hour light/dark cycle (lights on at 7 a.m.) and free access to food and water except during the test periods. The animals were kept and subjected to behavior and motor tests at the Health Science Experimental Laboratory (LESC) at the Jardim Botânico Campus – UFPR.

Groups and drugs: According to the medication used as prophylactic treatment, the animals were divided into five groups (Figure 1): isotonic saline solution (ISS) 0.9% (Group A, n=19), propranolol 1.65 mg/kg (Group B, n=19), topiramate 1.65 mg/kg (Group C, n=20), flunarizine 0.33 mg/kg (Group D, n=20), and amitriptyline 1.65 mg/kg (Group E, n=20). All animals received daily dosages of the prophylactic drug between 9-10 a.m. The injections were made intraperitoneally by diluting the drug in 1 ml of ISS in the first five days. On the sixth day, each group was dichotomized into subgroups according to the drug used to simulate an acute treatment: SS 0.4 mg/kg (Subgroup 1) or 1 ml of 0.9% ISS (Subgroup 2). Again, the drugs were administered intraperitoneally. The animals received the acute treatment fifteen minutes before the motor function tests.

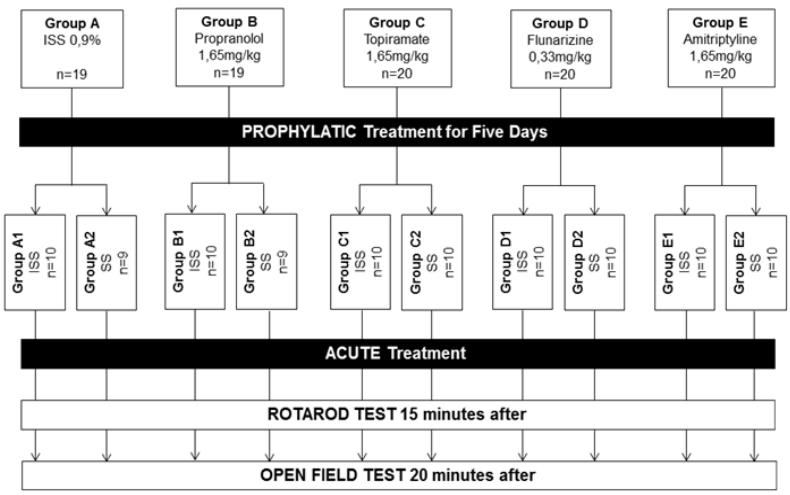

Figure 1. Study design. Preventive treatment groups: (A) isotonic saline solution (ISS), (B) propranolol, (C) topiramate, (D) flunarizine, and (E) amitriptyline. Acute treatment subgroups: (A, B, C, D, E-1) ISS, and (A, B, C, D, E-2) sumatriptan succinate (SS).

Randomization procedure: The animals were randomly assigned to each group following simple randomization.

Motor function evaluation: The evaluation was conducted using the rotarod and the open field tests 15 and 20 minutes after administering the SS or ISS, respectively. The rotarod test (Figure 2) is a performance evaluation that uses forced locomotion on a suspended rotating cylinder to assess parameters such as balance, coordination, and motor planning (7).

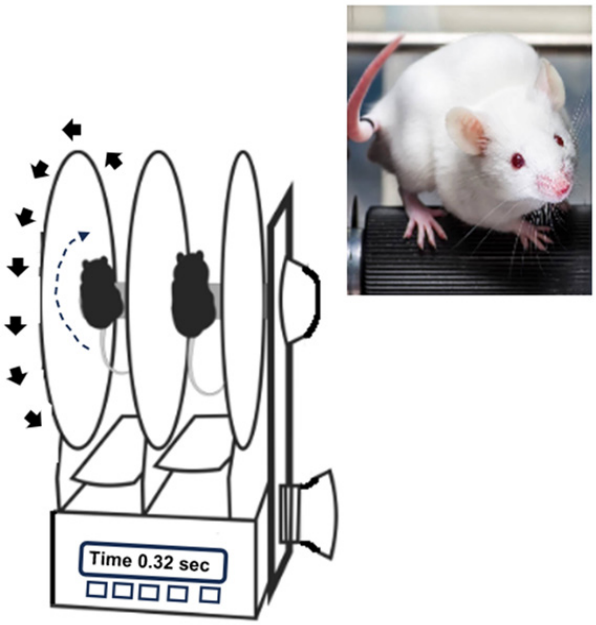

Figure 2. Rotarod test. Parameters such as balance, coordination, and motor planning are evaluated. We recorded the time spent in the rotating bar in three series of sixty seconds, using a constant speed of 16 rotations per minute (7,8).

The animal is placed on a horizontally oriented rotating rod, suspended to a height low enough not to hurt the animal but high enough to induce it to avoid falling. The technique, evaluation protocols, and the complete methodology followed previously published guidance (7,8). The assessment was based on the time spent on the rotating bar in three series of sixty seconds, using a constant speed of 16 rotations per minute. The open field test (Figure 3) evaluates animals' motor function and anxiety behavior (9). We used a circular arena with a diameter of 1 meter, a white floor divided into 19 quadrants, illuminated by a homogeneous light source. The animals were individually placed in the central area and allowed to explore the environment for 5 minutes. During this period, the following parameters were assessed: time to leave the central field (latency), number of quadrants in which the animal wandered (quadrants traversed), period of time the animal is stationary (immobility), and number of times the animal gets up (number of rearings).

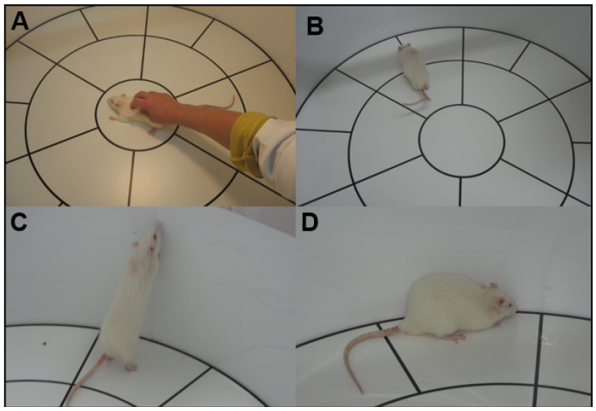

Figure 3. Open field test. The animals were individually placed in the central arena (A). We recorded the following parameters: time to leave the central field (latency), number of quadrants in which the animal wandered (quadrants transversed, B), number of rearings (C), and the total time the animal remained stationary (immobility, D) (9).

Blinding of the investigators: The researcher who applied the drugs did not participate in any other phase of this study. The investigator who conducted the tests did not know which animals belonged to the different groups. The association between drugs and results of the groups was revealed only at the end of the study.

Ethics committee and statistical treatment: All experiments and experimental procedures were conducted with the approval of the local ethics committee for animal research (Federal University of Parana). To compare the prophylactic drugs, we used the nonparametric Kruskal-Wallis test, and to compare the results between the groups that received acute treatment with ISS or SS we employed the nonparametric Mann-Whitney test. A p-value$<$0.05 was considered significant.

NC3Rs ARRIVE Guidelines 2013: All experimental procedures were conducted using the Animal Research Reporting of In Vivo Experiments (ARRIVE guidelines).

Results

Migraine prophylactic drugs influence on motor activity: Assessing the influence of migraine prophylactic drugs on the motor activity of the animals could be accomplished through statistical analysis of the data obtained in the subgroups that received only 0.9% ISS as acute treatment (subgroups A1, B1, C1, D1, and E1). The evaluation of the five subgroups (Table 1) showed statistically significant differences in length of stay on the rotating rod among them ($p=0.013$) but not in the parameters of the open field.

A comparison of the results obtained on the rotarod test between pairs of drugs (Table 2) showed that the amitriptyline group (E1, 57 ± 4.5) presented higher scores when compared with the propranolol (B1, 47.2 ± 13.9, $p=0.042$)

Table 1. Descriptive data and comparisons among subgroups using different prophylactic drugs associated with isotonic saline solution as the acute treatment

Test	Preventive drug	N	Mean	Median	Minimum	Maximum	SD	P value*
Rotarod (seconds)	ISS (A1)	10	58.5	60	50.7	60	3.2	0.013
	Propranolol (B1)	10	47.2	50.2	19	60	13.9	
	Topiramate (C1)	10	53.2	57.3	34.7	60	9.1	
	Flunarizine (D1)	10	47.8	48.3	33.3	60	8.8	
	Amitriptyline (E1)	10	57	60	48.7	60	4.5	
Open Field - Latency (seconds)	ISS (A1)	10	4.2	4	1	8	2.4	0.468
	Propranolol (B1)	10	14.9	4	2	70	21.7	
	Topiramate (C1)	10	62.3	3	1	505	158.2	
	Flunarizine (D1)	10	3.3	2	1	8	2.6	
	Amitriptyline (E1)	10	21.1	3.5	1	118	37.1	
Open Field - Quadrants Traversed (number)	ISS (A1)	10	54.3	52	17	87	23	0.552
	Propranolol (B1)	10	46.1	37	2	106	34.3	
	Topiramate (C1)	10	52.6	59	3	74	20.7	
	Flunarizine (D1)	10	58.9	52,5	41	92	19.5	
	Amitriptyline (E1)	10	50.5	42	1	156	41	
Open Field - Number of Rearings	ISS (A1)	10	14.8	13.5	4	40	10.8	0.752
	Propranolol (B1)	10	14.3	14	5	24	6.1	
	Topiramate (C1)	10	19	13.5	7	61	15.8	
	Flunarizine (D1)	10	13.2	13	6	20	3.9	
	Amitriptyline (E1)	10	10.6	11	4	16	3.6	
Open Field - Immobility (seconds)	ISS (A1)	10	148.6	129.5	88	239	50.3	0.752
	Propranolol (B1)	10	152.2	148	79	248	51.7	
	Topiramate (C1)	10	150.8	149	68	204	44.6	
	Flunarizine (D1)	10	152.8	169	94	197	37.4	
	Amitriptyline (E1)	10	165.3	181.5	60	213	50.2	

* Nonparametric Kruskal-Wallis test with the significance level set at 5%. Statistically significant results are indicated in bold. ISS: isotonic saline solution, SD: standard deviation

and flunarizine groups (D1, 47.8±8.8, p=0.012), which suggests a significant difference in motor influence between amitriptyline and propranolol/flunarizine. However, there was no difference between the amitriptyline and ISS (A1, 58.5±3.2) groups, which suggests that amitriptyline does not interfere with motor activity. The comparison between ISS and propranolol, nevertheless, demonstrates that this drug interfered consistently with motor activity (p=0.006). Similarly, when we compared the ISS and flunarizine groups, it seemed that this drug also interfered with this domain (p=0.002). Finally, although the animals treated with topiramate (C1, 53.2±9.1) presented lower scores than those that received ISS, the difference did not reach statistical significance (p=0.083).

Table 2. Pair-wise comparison of motor activity among groups using different prophylactic drugs and treated acutely with isotonic saline solution

Combination of drugs	P value*
Amitriptyline (E1) vs. propranolol (B1)	**0.042**
Amitriptyline (E1) vs. topiramate (C1)	0.319
Amitriptyline (E1) vs. ISS (A1)	0.449
Amitriptyline (E1) vs. flunarizine (D1)	**0.012**
Propranolol (B1) vs. topiramate (C1)	0.282
Propranolol (B1) vs. ISS (A1)	**0.006**
Propranolol (B1) vs. flunarizine (D1)	0.611
Topiramate (C1) vs. ISS (A1)	0.083
Topiramate (C1) vs. flunarizine (D1)	0.116
ISS (A1) vs. flunarizine (D1)	**0.002**

* Nonparametric Kruskal-Wallis test with the significance level set at 5%. Statistically significant results are indicated in bold.
ISS: isotonic saline solution

Influence of the migraine prophylactic drugs in the motor activity after using sumatriptan succinate: Assessing the influence of the association between prophylactic drugs (ISS, propranolol, topiramate, flunarizine, amitriptyline) and SS in the motor activity could be accomplished through the analysis of the data obtained in the subgroups who received SS as an acute treatment (subgroups A2, B2, C2, D2, and E2). The five groups' evaluation showed no statistically significant difference between the drugs in the rotarod or open field tests (Table 3).

Comparison of the motor activity influence of migraine prophylactic drugs in association with acute treatment with ISS vs. SS: To evaluate the influence of SS in association with each of the prophylactic drugs, we performed a nonparametric test, and then the same group could only diverge regarding the acute treatment (e.g., propranolol + ISS vs. propranolol + SS, Table 4). In the rotarod test, there was no potentiation or reduction of results with or without SS, demonstrating that this drug alone could not change the behavior or motor activity when used in association with migraine prophylactic drugs.

Discussion

This study showed that some drugs used for the preventive treatment of migraine could reduce motor activity (propranolol and flunarizine) while others did not interfere with it (amitriptyline and topiramate). Our findings also suggested that the association of these drugs with SS alone does not alter motor responses.

Sumatriptan succinate was developed over 20 years ago and acts as a 5HT1B-1D agonist, the first drug specifically developed for the acute treatment of migraine. Fatigue

Table 3. Descriptive data and comparisons among subgroups using different prophylactic drugs associated with sumatriptan succinate as the acute treatment

Test	Preventive drug	N	Mean	Median	Minimum	Maximum	SD	P value*
Rotarod (seconds)	ISS (A2)	9	53.4	57.7	38	60	7.7	0.984
	Propranolol (B2)	9	49.3	60	15	60	16.7	
	Topiramate (C2)	10	48.8	50.5	22.7	60	12.4	
	Flunarizine (D2)	10	51.6	59.3	23	60	13	
	Amitriptyline (E2)	10	51.6	54.8	18.7	60	12.7	
Open Field - Latency (seconds)	ISS (A2)	9	4.4	2	1	10	3.6	0.789
	Propranolol (B2)	9	13.6	6	1	52	18.5	
	Topiramate (C2)	10	6.9	5	1	17	6.1	
	Flunarizine (D2)	10	6.1	5	3	17	4.3	
	Amitriptyline (E2)	10	17.8	5	1	66	24.4	
Open Field - Quadrants Transversed (number)	ISS (A2)	9	48.1	57	10	73	23.5	0.894
	Propranolol (B2)	9	48.9	59	4	98	34.9	
	Topiramate (C2)	10	62.8	43.5	30	114	33.3	
	Flunarizine (D2)	10	63.8	60.5	37	111	24.3	
	Amitriptyline (E2)	10	66	57.5	1	156	54.9	
Open Field - Number of Rearings	ISS (A2)	9	15.7	15	2	28	8	0.438
	Propranolol (B2)	9	11.2	8	2	23	7	
	Topiramate (C2)	10	14.5	11	7	27	7.9	
	Flunarizine (D2)	10	12.7	12.5	4	28	7.4	
	Amitriptyline (E2)	10	21.7	16.5	6	57	16.1	
Open Field - Immobility (seconds)	ISS (A2)	9	157.4	166	67	235	60.9	0.567
	Propranolol (B2)	9	144.1	107	60	259	78.5	
	Topiramate (C2)	10	141.4	145.5	43	223	69.9	
	Flunarizine (D2)	10	164	162.5	105	225	40.3	
	Amitriptyline (E2)	10	120.2	133	27	202	57.2	

* Nonparametric Kruskal-Wallis test with the significance level set at 5%. Statistically significant results are indicated in bold. ISS: isotonic saline solution, SD: standard deviation

after using it has been described and is related to alterations in the mitochondrial metabolism by decreasing the oxygen supply to the peripheral skeletal muscles, inducing an energetic reduction, substantially altering muscle strength, and causing muscle pain (10). The SS-induced peripheral vasoconstriction potentially plays a role in reducing the oxygen supply through a mechanism of serotonin modulation.

Previous studies using sumatriptan have suggested that 5-hydroxytryptamine (5-HT) was involved as a central neurotransmitter in anxiety modulation in a central punishment system (11). The specific serotonergic site responsible for the anxiolytic effect appears to be centered around the 5HT3 system, although a subtle component involving the 5HT1B site is possible (12,13). In a case report, a patient with social anxiety showed complete improvement 40 minutes after taking a serotonin agonist 5HT1B/D (almotriptan), an effect lasting eight hours on more than one occasion (14).

In experimental trials, administering a selective 5-HT1B receptor agonist 3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3,2-b]pyridine (CP 94,253; 1-5.6 mg/kg) dose-dependently decreased the amount of exploration on the open arms of the plus-maze without altering overall motor activity (15). This 5-HT1B agonist-induced increase in anxiety-like behavior was dose-dependently reversed by the coadministration of the selective 5-HT1B/1D receptor antagonist 2'-methyl-4'-(5-methyl[1,2,4]oxadiazol-3-yl)-biphenyl]-amide (GR 127,935). These results showed that SS might have another action site besides 5HT1B, able to induce the anxiolytic effect (15). Other experimental studies in mice demonstrated that 5HT1B agonists present an anxiolytic effect (13).

Our study showed no motor effect of SS or its combination with major migraine preventive drugs. We cannot claim that the current study showed an effect on metacognition. We can, however, affirm that sumatriptan did not alter motor function.

References

1. Bigal ME, Lipton RB, Stewart WF. The epidemiology and impact of migraine. Curr Neurol Neurosci Rep. 2004 Mar;4(2):98–104. DOI: 10.1007/s11910-004-0022-8
2. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000 Sep;55(6):754–62. DOI: 10.1212/wnl.55.6.754
3. [Recommendations for prophylactic treatment of migraine: Consensus of the Sociedade Brasileira de Cefaléia]. Arq Neuropsiquiatr. 2002 Mar;60(1):159–69. DOIi: 10.1590/s0004-282x2002000100030
4. Rizzo M. Impaired driving from medical conditions: a 70-year-old man trying to decide if he should continue driving. JAMA. 2011 Mar;305(10):1018–26. DOI: 10.1001/jama.2011.252
5. al-Qassab HK, Findley LJ. Comparison of propranolol LA 80 mg and propranolol LA 160 mg in migraine prophylaxis: a placebo controlled study. Cephalalgia. 1993 Apr;13(2):128–31. DOI: 10.1046/j.1468-2982.1993.1302128.x
6. Ye Q, Yan LY, Xue LJ, Wang Q, Zhou ZK, Xiao H, et al. Flunarizine blocks voltage-gated Na(+) and Ca(2+) currents in cultured rat cortical neurons: A possible locus of action in the prevention of migraine. Neurosci Lett. 2011 Jan;487(3):394–9. DOI: 10.1016/j.neulet.2010.10.064
7. Jones BJ, Roberts DJ. The quantiative measurement of motor inco-ordination in naive mice using an acelerating rotarod. J Pharm Pharmacol. 1968 Apr;20(4):302–4. DOI: 10.1111/j.2042-7158.1968.tb09743.x
8. Ali BH, Bashir AK, Tanira MO. Some effects of Cassia italica on the central nervous system in mice. J Pharm Pharmacol. 1997 May;49(5):500–4. DOI: 10.1111/j.2042-7158.1997.tb06831.x
9. Crawley JN. Exploratory behavior models of anxiety in mice. Neurosci Biobehav Rev. 1985;9(1):37–44. DOI: 10.1016/0149-7634(85)90030-2
10. Boska MD, Welch KM, Schultz L, Nelson J. Effects of the anti-migraine drug sumatriptan on muscle energy metabolism: relationship to side-effects. Cephalalgia. 2000 Feb;20(1):39–44. DOI: 10.1046/j.1468-2982.2000.00009.x
11. Amital D, Fostick L, Sasson Y, Kindler S, Amital H, Zohar J. Anxiogenic effects of Sumatriptan in panic disorder: a double-blind, placebo-controlled study. Eur Neuropsychopharmacol. 2005 May;15(3):279–82. DOI: 10.1016/j.euroneuro.2004.12.002
12. Gardner CR. Potential use of drugs modulating 5HT activity in the treatment of anxiety. Gen Pharmacol. 1988;19(3):347–56. DOI: 10.1016/0306-3623(88)90027-4
13. Tatarczyńska E, Kłodzińska A, Stachowicz K, Chojnacka-Wójcik E. Effects of a selective 5-HT1B receptor agonist and antagonists in animal models of anxiety and depression. Behavioural pharmacology. 2004 Dec;15(8):523–34. DOI: 10.1097/00008877-200412000-00001
14. Morelli N, Gori S, Choub A, Maluccio MR, Orlandi G, Guazzelli M, et al. Do 5HT1B/1D receptor agonists have an effect on mood and anxiety disorders? Vol. 27, Cephalalgia: an international journal of headache. England; 2007. p. 471–2. DOI: 10.1111/j.1468-2982.2007.01294.x
15. Lin D, Parsons LH. Anxiogenic-like effect of serotonin(1B) receptor stimulation in the rat elevated plus-maze. Pharmacol Biochem Behav. 2002 Apr;71(4):581–7. DOI: 10.1016/s0091-3057(01)00712-2

Author contributions: EMN, EJP, conception and design; EJP, GAC, MCS, LPA, CRB, GR, GCG, Literature search; EJP, MATU analysis and interpretation of data; EMN, EJP, PAK, GAC, MCS, LPA, CRB, GR, GCG, drafting the manuscript; EMN, MATU, EJP, PAK, GAC, MCS, LPA, CRB, GR, GCG, revising it for intellectual content; EMN, MATU, EJP, PAK, GAC, MCS, LPA, CRB, GR, GCG, final approval of the completed manuscript.

Conflict interest: The authors declare that they have no conflict interests.

Funding: No