

Amitriptyline: Useful for the prophylactic treatment of migraine?

Amitriptilina: Útil para o tratamento profilático da enxaqueca?

Amitriptilina: ¿Útil para el tratamiento profiláctico de la migraña?

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Abstract

Migraine is a type of headache described by recurrent attacks that may be accompanied by some symptoms, such as nausea, vomiting, phonophobia, among other conditions. About 1 billion people in the world could come into existence. Some measurements are recognized for the treatment of use, as measurements are made appropriately with cost drugs. Amitriptyline has become a great alternative for the prophylactic treatment of migraine, its metabolization is extensively in the liver and its analgesic effect is linked to the ability to modulate mood or modulate the excitability of neurons that transmit pain signals from the dura mater. This study is an integrative literature review. A search key was created, and the search was performed in the Web of Science (WoS-all databases). A temporal search was carried out between the years 2018 to June 2022, without language restriction. Tools such as MapChart were used to create the worldwide distribution map based on the corresponding author. 100 articles were rescued from the Web of Science, of which only 20 were chosen to compose the final table, due to their high relevance and sensitivity in the investigated topic. Migraine prevention for patients is critical, as it can reduce stigma and enhance quality of life.

Keywords: Amitriptyline; Migraine; Treatment.

Resumo

Enxaqueca é um tipo de cefaléia descrita por crises recorrentes que podem vir acompanhada de alguns sintomas, como náuseas, vômito fonofobia, entre outras condições. Há cerca de 1 bilhão de pessoas no mundo com enxaqueca. Algumas medidas são necessárias para o tratamento da enxaqueca, uma dessas medidas é fazendo o uso apropriado com drogas de custo baixo. A amitriptilina tornou-se uma ótima alternativa para o tratamento profilático da enxaqueca, sua metabolização é extensivamente no fígado e seu efeito analgésico está ligado à capacidade de modular o humor ou modular a excitabilidade de neurônios que transmitem sinais de dor da dura-máter. Este estudo trata-se de uma revisão integrativa da literatura. Foi criada uma combinação de chaves de busca e a busca foi realizada na Web of Science (WoS-all databases). Realizou-se uma busca temporal entre os anos de 2018 a junho de 2022, sem restrição de idiomas. Ferramentas como o MapChart foram utilizadas para a criação do mapa de distribuição mundial com base no autor de correspondência. Foram resgatados 100 artigos da Web of Science, destes apenas 20 foram eleitos para compor a tabela final, devido à alta relevância e sensibilidade no tema investigado. A prevenção da enxaqueca para os pacientes é fundamental, pois pode reduzir o estigma e fomentar a qualidade de vida. Demonstramos através desta revisão que a amitriptilina pode ter um papel profilático primário em pacientes com enxaqueca, no entanto, a realização de novos estudos é essencial, uma vez que o uso da amitriptilina pode promover efeitos adversos em faixas etárias diferentes.

Palavras-chave: Amitriptilina; Enxaqueca; Tratamento.

Resumen

La migraña es un tipo de dolor de cabeza descrito por ataques recurrentes que pueden estar acompañados de algunos síntomas, como náuseas, vómitos, fonofobia, entre otras condiciones. Hay alrededor de mil millones de personas en el mundo con migrañas. Algunas medidas son necesarias para el tratamiento de la migraña, una de estas medidas es hacer el uso adecuado con medicamentos de bajo costo. Incluir o resumo em espanhol. La amitriptilina se ha convertido en una gran alternativa para el tratamiento profilático de la migraña, su metabolización es extensa en el hígado y su efecto analgésico está ligado a la capacidad de modular el estado de ánimo o modular la excitabilidad de las neuronas que transmiten señales de dolor desde la duramadre. Este estudio es una revisión integrativa de la literatura. Se creó una combinación de claves de búsqueda y la búsqueda se realizó en Web of Science (WoS-all las bases de datos). Se realizó una búsqueda temporal entre los años 2018 a junio de 2022, sin restricción de idioma. Se utilizaron herramientas como MapChart para crear el mapa de distribución mundial basado en el autor correspondiente. Se recuperaron 100 artículos de la Web of Science, de los cuales solo 20 fueron elegidos para componer la tabla final, debido a la alta relevancia y sensibilidad del tema investigado. La prevención de la migraña para los pacientes es fundamental, ya que puede reducir el estigma y mejorar la calidad de vida. Demostramos a través de esta revisión que la amitriptilina puede tener un papel profilático primario en pacientes con migraña, sin embargo, es esencial realizar más estudios, ya que el uso de amitriptilina puede promover efectos adversos en diferentes grupos de edad.

Palabras clave: Amitriptilina; Migrainã; Tratamiento.

1. Introduction

Migraine is a chronic neurological disease, evidenced by the frequency and severity of headaches, gastrointestinal symptoms and transient neurological symptoms that generate considerable suffering and negative impacts on physical and mental health, as well as on school performance and quality of life of patients (Silberstein et al., 2015). This disabling disease is one of the most common brain disorders in the world and a leading cause of emergency and outpatient consultations, being a major public health problem worldwide (Olla et al., 2020).

In the world, there are about one billion individuals affected by this disease, distributed in countries of North America, South and Central America, Europe, Asia and Africa (Hmoud et al., 2021). In these regions, 30% or more of adults aged 18 to 65 years reported migraine, additionally migraine is common among children and adolescents and has a prevalence of 1 to 3% in children aged 3 to 7 years, 4 to 11% in children aged 7 to 11 years and 8 to 23% at 15 years (Oskoui et al., 2019).

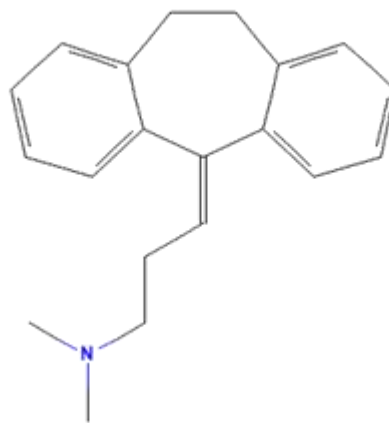
For the adequate treatment of migraine, some important measures are necessary, including clinical evaluation by qualified and trained health professionals, accurate and rapid diagnosis, appropriate treatment with low-cost drugs, changes in the patient's lifestyle. Pharmacological treatment of migraine can be acute, also regarded as abortifacient or prophylactic, and patients with frequent and severe headaches require both approaches. Preventive therapy is used to reduce the duration, frequency, or severity of attacks (Silberstein et al., 2015). For the treatment of migraine drugs can be divided daily whether or

not headache is present to reduce the frequency and severity of attacks (Goadsby et al., 2002 and Becker et al., 2015).

Among the main classes of drugs that can be used to treat migraines such as analgesics, antiemetics, prophylactic drugs and specific anti-migraine drugs, drugs for the preventive treatment of migraine with well-documented effectiveness are divalproex, topiramate, beta-blockers and amitriptyline. Among these drugs, amitriptyline deserves to be highlighted, extensively used for this purpose, and its choice is based on the headache profile, as well as the presence or absence of coexisting disorders (Silberstein, 2009).

Amitriptyline is a classic tricyclic antidepressant (TCA) widely used to treat chronic neuropathic pain due to nerve damage and fibromyalgia and is also recommended in many guidelines (Couch et al., 1979; Moore et al., 2012). It is a drug approved by the Food and Drug Administration (FDA) to treat depression in adults. The FDA also indicates in cases of anxiety, insomnia, post-traumatic stress disorder, irritable bowel syndrome, interstitial cystitis or also called bladder pain syndrome, post-herpetic neuralgia, drooling and migraine prophylaxis (Moore et al., 2012; Obata et al., 2017; Schnider et al., 2019; Thour et al., 2019).

Figure 1 - Molecular structure of amitriptyline.



Source: National Biotechnology Information Center, PubChem (2022).

Amitriptyline is one of the main drugs used for migraine as prophylaxis (Hmoud et al., 2021). Its analgesic effects are linked to its ability to modulate mood and/or modulate the excitability of long-lasting neurons that transmit pain signals from the dura mater (Kang et al., 2018). After administration, amitriptyline is extensively metabolized in the liver to the pharmacologically active metabolite nortriptyline. The terminal elimination half-life of amitriptyline ranges from 12.9 to 36.1 hours (Bryson et al., 1996).

Given the relevance of the topic addressed to public health, as well as the high involvement and impact of migraine on the quality of life of individuals, this study aims to review the most recent scientific findings available in the literature on the usefulness of amitriptyline as migraine prophylaxis.

2. Methodology

2.1 Data and search strategy

This integrative review was conducted in accordance with the guidelines of “Writing Integrative Literature Reviews: Guidelines and Examples” (Torraco, 2005), “The integrative review: updated methodology” (Whittemore and Knaf, 2005) and “Writing Integrative Reviews of the Literature: Methods and Purposes” (Torraco, 2016). Two researchers independently

searched the Web of Science database, without no language restrictions, and articles published from January 2018 to July 2022. The search strategy was as follows:

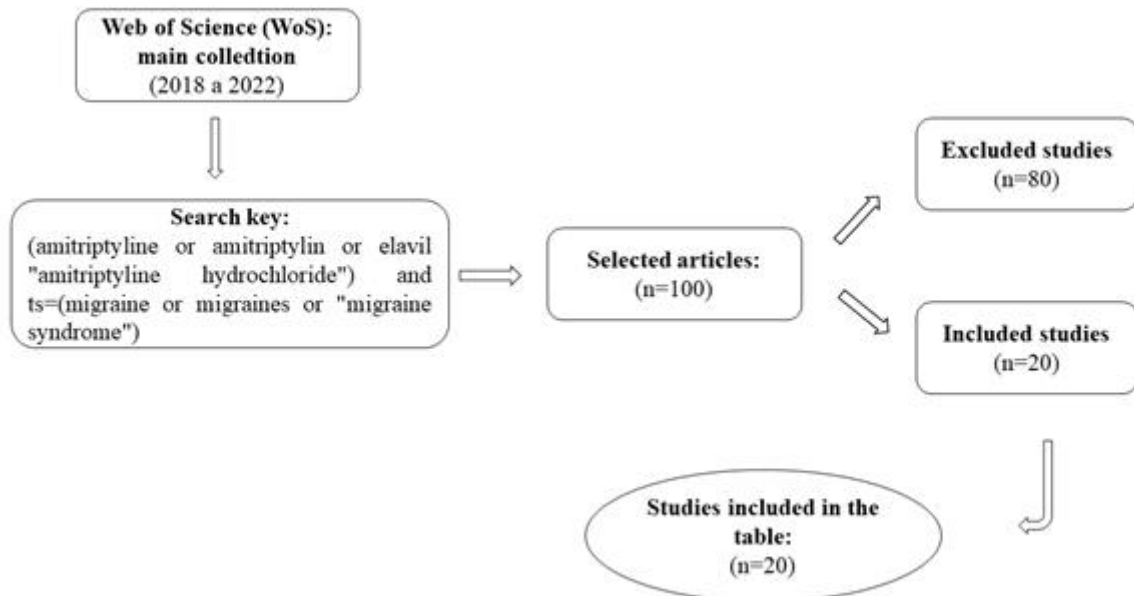
- (1) ts=(amitriptyline or amitriptylin or elavil or "amitriptyline hydrochloride")
- (2) ts=(migraine or migraines or "migraine syndrome").
- (3) 1 and 2.

2.2 Study selection criteria - inclusion and exclusion

In this study, after retrieving the manuscripts from the database, they were reviewed for eligibility. After evaluation, studies including letters, meeting summaries, mini reviews, duplicate studies were removed from the retrieved records. On the other hand, we included in our study, (1) published articles from all identified clinical trials of patients who received amitriptyline to treat migraine; (2) studies that compared the effectiveness of treatment regimens for preventing new migraine attacks; (3) migraine diagnosed based on International Headache Society (IHS) diagnostic criteria or confirmed by board-certified neurologists; and (4) trials that reported efficacy results with data that could be extracted. All disagreements were resolved by consensus with the help of a third reviewer.

After selecting these studies, a world map was created with the help of MapChart (Figure 2). On the map, the continents, and countries of origin of the authors of correspondence were identified, as well as the number of publications in each region. These were represented by colors. On the other hand, studies that did not evaluate the action of amitriptyline against migraine in any scenario were excluded, as well as articles outside the proposed study period, not being listed on the world map.

Flowchart 1 - Methodological schedule.



Source: Authors (2022).

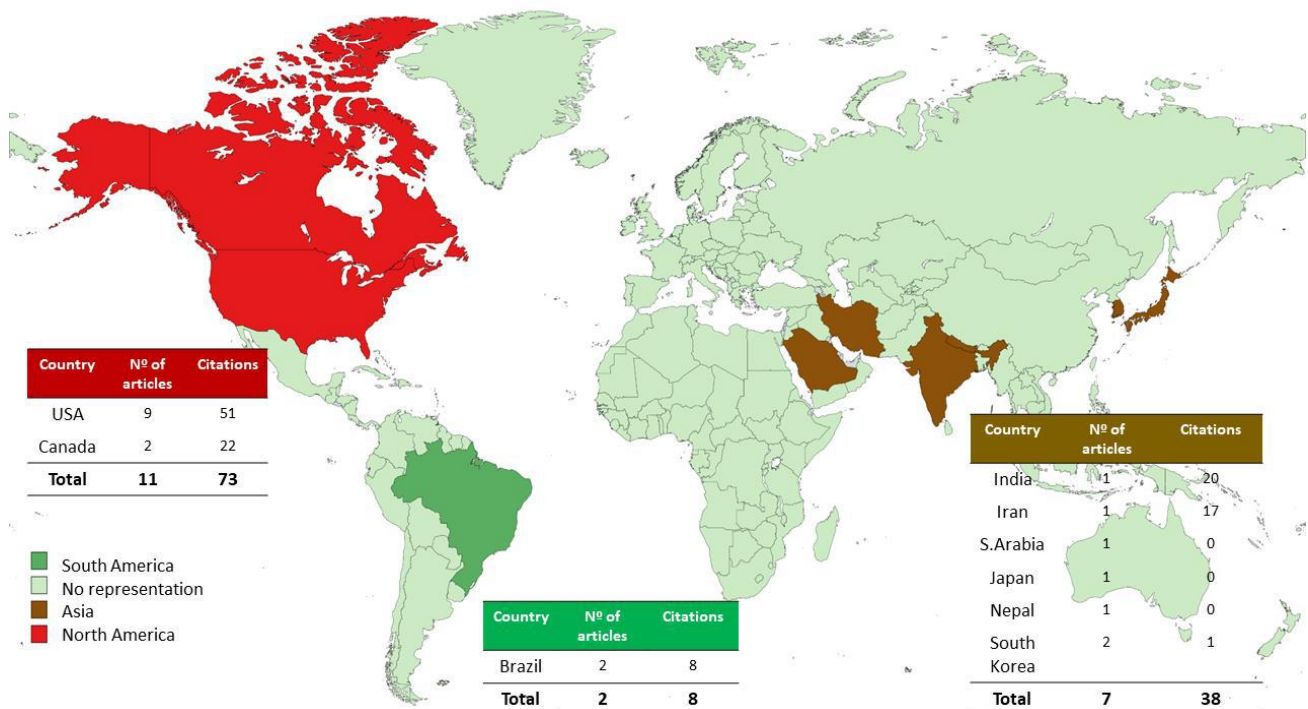
3. Results and Discussion

Amitriptyline has been effective in tension headaches since mid-1964, and its beneficial effect on migraine has been

reported since 1969 (Gomersall et al., 1973). This medication has been one of the mainstays of migraine prophylaxis for over 35 years and is currently one of the most used drugs for this purpose. Despite this, there are still few controlled clinical studies of amitriptyline as a therapeutic agent in the prevention of migraine (Couch et al., 2011).

In this sense, in our study, from the search carried out in the Web of Science database from 2018 to 2022, 100 articles were retrieved, and after applying the inclusion criteria, 80 studies were excluded, as they did not provide information concise information on the action of amitriptyline in migraine prophylaxis, on the other hand, 20 studies had a high association between the keywords, being included in the search.

Figure 2 - World map: the articles selected for inclusion in this review.



Source: Authors (2022).

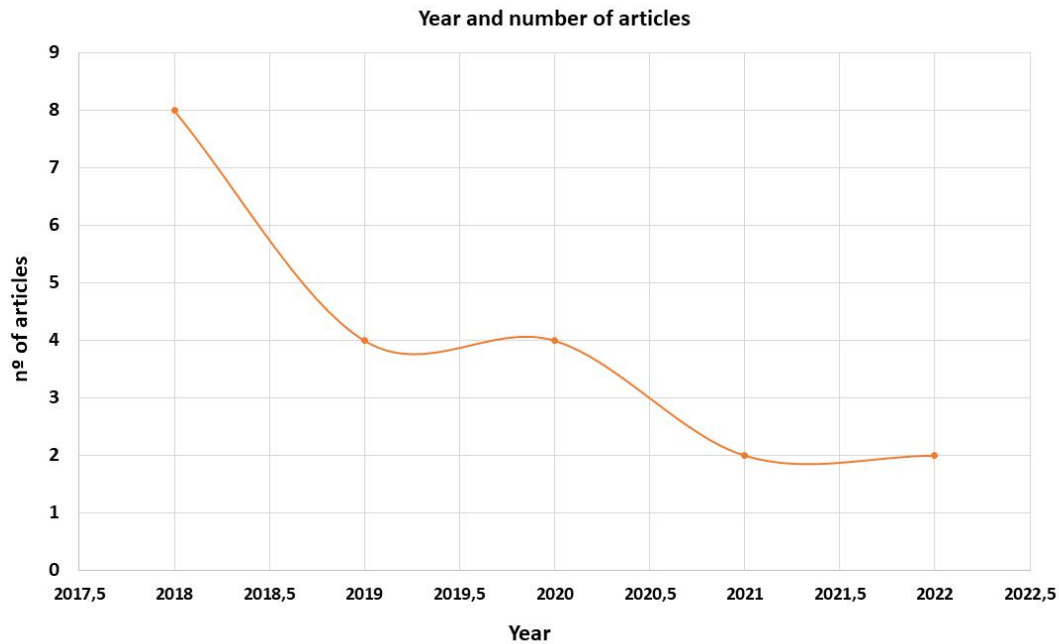
According to the world map (Figure 2), of the 20 studies included in the survey, 11 studies originated in North America, 7 in Asia, 2 in South America. Of the articles originating in South America, 9 were from the United States and 2 from Canada. Together, these articles presented 51 citations in the period evaluated. On the Asian continent, India is the country with the highest number of citations (20), followed by Iran with 17 citations. From these results, it is possible to observe that despite North America having a greater number of published articles and still having a considerable number of citations together, the countries India, Iran and Canada stand out, as both have 1, 1 and 2 articles. with an extremely higher number of citations compared to the United States.

We believe that these results are due to the scientific relevance of the works, since the articles from India, Iran and Canada highlight the action of amitriptyline in children diagnosed with migraine, and also relate to other substances extensively used in experimental research such as melatonin. Additionally, it is noteworthy that the article from India was published in 2018 and the research from the United States was published mostly in 2021.

In this context, of the studies included in the research, 8 were published in 2018, 4 in 2019, 4 in 2020, 2 in 2021 and 2 in 2022 (Graph 1). Additionally, 8 studies were classified as literature review, 7 in vivo research, 2 case reports, 2 systematic reviews and 1 observational study (Table 1).

Studies by Bruno et al. (2018), Fallah et al. (2018), Kang et al. (2018), Tripathi et al. (2018), Dhungana et al. (2021), Reidy et al. (2022), Rettig et al. (2022) demonstrated through in vivo trials that amitriptyline is an effective drug for migraine prophylaxis, but its use depends heavily on the age group of the population studied.

Graph 1 – Year and number of articles published in the study period.



Fonte: Authors (2022).

Table 1 - Description of selected studies.

nº	Author / Year	DOI / Link	Kind of study	Results
1	Hmoun et al., 2021	10.7759/cureus.12848	Case report	Amitriptyline may be used in neurology as a prophylactic treatment to reduce the severity and frequency of migraine attacks.
2	Bruno et al., 2018	10.1590/0004-282X20180023	<i>In vivo</i> study	Amitriptyline was significantly more effective in reducing the frequency of migraine attacks without aura than NTL-tss and non-occlusal splint.
3	Fallah et al., 2018	https://pubmed.ncbi.nlm.nih.gov/29379562/	<i>In vivo</i> study	Amitriptyline is effective and safe in pediatric migraine prophylaxis.
4	Burch et al., 2019	10.1007/s11940-019-0557-2	Literature review	Amitriptyline has the best evidence for use in migraine prevention.
5	Kang et al., 2018	10.1016/j.ejphar.2018.09.006	<i>In vivo</i> study	Diverse amitriptyline-mediated modulation of TTX-R channels was responsible for its prophylactic efficacy for migraine attacks.
6	Qureshi et al., 2019	10.1007/s11940-019-0560-7	Literature review	Childhood and adolescent migraine prevention study (CHAMP) did not endorse the superiority of amitriptyline over placebo.
7	Rettig et al., 2022	10.1007/s10880-021-09782-4	<i>In vivo</i> study	Amitriptyline is a TCA often prescribed as a first-line preventative drug.
8	Oskoui et al., 2019	10.1111/head.13625	Systematic review	Children with migraine who receive amitriptyline plus cognitive behavioral therapy are more likely than those who receive amitriptyline plus headache

				education to have a reduction in headache frequency.
9	Dhungana et al., 2021	https://www.neurologyasia.org/articles/neuroasia-2021-26(1)-107.pdf	<i>In vivo</i> study	Amitriptyline was effective for migraine prophylaxis in the Nepalese population.
10	Von Brevem et al., 2020	10.1055/s-0039-3402067	Literature review	Frequent attacks may warrant pharmacological prophylaxis with amitriptyline.
11	Naito et al., 2018	10.1111/ncn3.12209	Observational	The predictive index obtained may represent a suitable scoring system for negative responses in patients using amitriptyline.
12	Rao et al., 2020	10.1080/14737175.2020.1797493	Literature review	Patients who received amitriptyline or topiramate had higher rates of adverse effects.
13	Kacperski et al., 2020	10.1007/s40272-020-00418-y	Literature review	Amitriptyline continues to have more data on its use for the prevention of migraine in children, but this may soon change with the development of controlled studies of new pharmacological treatments.
14	Burch et al., 2019	10.1016/j.jnc1.2018.09.004	Literature review	Amitriptyline may also be considered for preventive treatment of migraine during pregnancy.
15	Santos et al., 2018	10.1016/j.jocn.2018.10.013	Case report	Previous use of abortifacient or prophylactic therapies including amitriptyline failed due to lack of efficacy or side effects, especially vomiting.
16	Reidy et al., 2022	10.1177/03331024211033551	<i>In vivo</i> study	Amitriptyline is hypothesized to have no greater clinical benefit over placebo in this migraine trajectory analysis.
17	Khrizman et al., 2018	10.3928/19382359-20180129-02	Literature review	The well-designed CHAMP provided a negative result on the use of amitriptyline versus placebo.
18	Tripathi et al., 2018	10.1080/00207454.2017.1374959	<i>In vivo</i> study	After treatment, either by amitriptyline or by rTMS, oxidative stress parameters were significantly altered.
19	Im et al., 2020	10.5124/jkma.2020.63.10.644	Literature review	Amitriptyline is recommended for migraine prophylaxis.
20	Arruda et al., 2018	10.1080/14737175.2018.1438191	Systematic review	The combined use of amitriptyline with CBT for children and adolescents with chronic migraine is supported by an RCT.

Source: Authors (2022).

In this context, migraine is a progressive disease, which can be associated with a higher incidence of cerebral infarctions, and this may require preventive treatments with daily medications, even when the patient has a low frequency of attacks. In addition, it is a recurrent disease among young people, adults and children, and there is an extreme need to identify risk factors, thus enabling the use of appropriate therapy for the treatment of the disease (Arruda et al., 2018).

According to Arruda et al. (2018), the use of amitriptyline combined with Cognitive Behavior Therapy (CBT) for chronic migraine may constitute an effective alternative in the fight against migraine. However, Naito et al. (2018) report that the predictive index obtained may represent negative responses for patients when using amitriptyline. We believe that this difference between the studies was due to the difference in treatment time, dose and subjects treated in each study. Additionally, regardless of the medication indicated for the treatment of migraine, these should be started in small doses, and preferably with the use of a drug, that is, monotherapy for the simplest cases of treatment to ensure the safety and efficacy of the treatment.

In this sense, the tricyclic derivative amitriptyline is an antidepressant widely used in clinical practice to treat migraine. For this purpose, the initial doses of amitriptyline should be low and may be increased after 5-7 days if side effects such as vertigo syndrome, increased appetite, weight gain, drowsiness, dry mouth and constipation are not observed. However, as the doses required for migraine prophylaxis are generally much lower than antidepressant doses, this medication is well tolerated if started slowly and progressively.

According to von Brevern et al. (2020), what justifies pharmacological prophylaxis with amitriptyline is its calming and sedative properties, as this antidepressant interferes with serotonin receptors, decreasing their uptake, leading to the availability of the neurotransmitter, also known as the “happiness hormone”, increasing the feeling of well-being and disposition, causing the migraine to improve.

In recent studies Reidy et al. (2022) pointed to the importance of amitriptyline in migraine prophylaxis, based on a clinical analysis. In other studies, Dhungana et al. (2021), Hmoun et al. (2021), Rettig et al. (2022) demonstrated excellent benefits of amitriptyline, including in specific populations such as children, in which clinical trials demonstrated that amitriptyline was effective for migraine prophylaxis. Furthermore, Rettig et al. (2022) evidence that amitriptyline can serve as a first-line preventive drug to treat migraine.

Although there is scientific evidence demonstrating the effectiveness of amitriptyline in the prevention of migraine, there is still a need for further clinical trials in individuals of all ages, since the update of amitriptyline for the preventive treatment of migraine is still completely established between the scientific community, due to the side effects presented by the drug. Kacperski et al. (2020) and Rao et al. (2020), showed that the adverse effects induced by amitriptyline may vary, depending on the duration of treatment and the clinical condition of the patient.

4. Conclusion

Our integrative review showed that the tricyclic antidepressant amitriptyline may have a primary prophylactic role in migraine patients. However, in view of the studies retrieved and included in the study, these results are far from robust. This warrants further large-scale research to explore the role of amitriptyline, particularly in a proportion of migraine patients. The prevention and/or treatment of migraine are essential for the patient, as they can reduce stigma and improve the patient's quality of life. Both the use of monotherapy or the combination of adjuvant treatments against migraine are important.

For the success of the treatment, the identification of the problem and the establishment of the appropriate treatment are fundamental. Among the drugs used to treat migraine, we highlight in this study amitriptyline, a drug recommended for the treatment of depression. However, at lower doses, it can reduce or stop migraine-related pain. This medicine acts on the central nervous system, increasing the production of serotonin by the brain, leading to an improvement in emotional state, regulating mood, sleep, appetite, and sensitivity to pain. However, amitriptyline may promote some adverse effects including drowsiness, reduced alertness, dizziness, altered taste, dry mouth, increased appetite, weight gain and in some cases headache.

Therefore, it recommends conducting future longitudinal clinical studies to ensure the safe use of amitriptyline for the treatment of migraine, in view of the side effects caused by its use. In addition, it is suggested the creation of new studies aiming to find pharmacological alternatives and primary prophylactic methods, in order to enable a better quality of life for individuals affected by migraine, with a smaller number of possible unwanted side effects.

References

- Arruda, M. A., Chevis, C. F., & Bigal, M. E. (2018). Recent advances in the management of chronic migraine in children. *Expert Review of Neurotherapeutics*, 18(3), 231-239.
- Becker, W. J. (2015). Acute migraine treatment in adults. *Headache: The Journal of Head and Face Pain*, 55(6), 778-793.

- Bruno, M. A., & Krymchantowski, A. V. (2018). Amitriptyline and intraoral devices for migraine prevention: a randomized comparative trial. *Arquivos de Neuro-Psiquiatria*, 76, 213-218.
- Bryson, H. M., & Wilde, M. I. (1996). Amitriptyline. *Drugs & aging*, 8(6), 459-476.
- Burch, R. (2019). Antidepressants for preventive treatment of migraine. *Current treatment options in neurology*, 21(4), 1-12.
- Burch, R. (2019). Headache in Pregnancy and the Puerperium. *Neurologic Clinics*, 37(1), 31-51.
- Centro Nacional de Informações de Biotecnologia (2022). Resumo do Composto pubchem para CID 11065, cloridrato de amitriptilina. Recuperado em 12 de julho de 2022 de <https://pubchem.ncbi.nlm.nih.gov/compound/11065>.
- Couch, J. R., & Amitriptyline Versus Placebo Study Group. (2011). Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. *Headache: The Journal of Head and Face Pain*, 51(1), 33-51.
- Couch, J. R., & Hassanein, R. S. (1979). Amitriptyline in migraine prophylaxis. *Archives of Neurology*, 36(11), 695-699.
- Fallah, R., Fazelishoroki, F., & Sekhvat, L. (2018). A randomized clinical trial comparing the efficacy of melatonin and amitriptyline in migraine prophylaxis of children. *Iranian journal of child neurology*, 12(1), 47.
- Gomersall, J. D., & Stuart, A. (1973). Amitriptyline in migraine prophylaxis: changes in pattern of attacks during a controlled clinical trial. *Journal of Neurology, Neurosurgery & Psychiatry*, 36(4), 684-690.
- Goadsby, P. J., Lipton, R. B., & Ferrari, M. D. (2002). Migraine—current understanding and treatment. *New England journal of medicine*, 346(4), 257-270.
- Hmoud, M., Al-Husayni, F., Alzahrani, A., Alharthi, A., & Alwafi, E. (2021). Hypertension Secondary to Amitriptyline Use as Prophylactic for Migraine in a 26-Year-Old Man. *Cureus*, 13(1).
- Im, H. J., & Cho, S. J. (2020). Pharmacotherapy of migraine prevention based on the assessment of headache. *Journal of the Korean Medical Association*, 63(10), 644-649.
- Kacperski, J., Green, A., & Qaiser, S. (2020). Management of chronic migraine in children and adolescents: a brief discussion on preventive therapies. *Pediatric Drugs*, 22(6), 635-643.
- Kang, I. S., Cho, J. H., Lee, M. G., & Jang, I. S. (2018). Modulation of tetrodotoxin-resistant Na⁺ channels by amitriptyline in dural afferent neurons. *European Journal of Pharmacology*, 838, 69-77.
- Khizrman, M., & Pakalnis, A. (2018). Management of pediatric migraine: current therapies. *Pediatric Annals*, 47(2), e55-e60.
- Mendes, K. D. S., Silveira, R. C. C. P., & Galvão, C. M. (2019). Uso de gerenciador de referências bibliográficas na seleção dos estudos primários em revisão interativa. *Revista Texto e Contexto Enfermagem*, 28 (1): e20170204.
- Mo, T., Mo, M. C., & Mo, S. P. O. (2021). A comparison between amitriptyline and divalproex in prophylactic treatment of episodic migraine: An open label study from Nepal. *Neurology Asia*, 26(1), 107-112.
- Moore, R. A., Derry, S., Aldington, D., Cole, P., & Wiffen, P. J. (2012). Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews*, (12).
- Naito, Y., Ishii, M., Ishibashi, M., Kasai, H., & Katoh, H. (2018). Negative predictors of clinical response to amitriptyline in Japanese patients with migraine. *Neurology and Clinical Neuroscience*, 6(5), 125-130.
- Obata, H. (2017). Analgesic mechanisms of antidepressants for neuropathic pain. *International journal of molecular sciences*, 18(11), 2483.
- Olla, D., Sawyer, J., Sommer, N., & Moore, J. B. (2020). Migraine treatment. *Clinics in plastic surgery*, 47(2), 295-303.
- Oskoui, M., Pringsheim, T., Billingshurst, L., Potrebic, S., Gersz, E. M., Gloss, D., ... & Hershey, A. D. (2019). Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*, 93(11), 500-509.
- Qureshi, M. H., Esper, G. J., & Bashir, F. F. (2019). When to consider prophylactic antimigraine therapy in children with migraine. *Current Treatment Options in Neurology*, 21(4), 1-7.
- Rao, R., & Hershey, A. D. (2020). An update on acute and preventive treatments for migraine in children and adolescents. *Expert Review of Neurotherapeutics*, 20(10), 1017-1027.
- Reidy, B. L., Peugh, J., Hershey, A. D., Coffey, C. S., Chamberlin, L. A., Ecklund, D. J., ... & Powers, S. W. (2022). Trajectory of treatment response in the child and adolescent migraine prevention (CHAMP) study: A randomized clinical trial. *Cephalalgia*, 42(1), 44-52.
- Rettig, E. K., Ergun, G., Warfield, J. R., Slater, S. K., LeCates, S. L., Kabbouche, M. A., ... & Powers, S. W. (2022). Predictors of improvement in pediatric chronic migraine: results from the cognitive-behavioral therapy and amitriptyline trial. *Journal of Clinical Psychology in Medical Settings*, 29(1), 113-119.
- Santos, C., & Weaver, D. F. (2018). Topically applied linoleic/linolenic acid for chronic migraine. *Journal of Clinical Neuroscience*, 58, 200-201.
- Schneider, J., Patterson, M., & Jimenez, X. F. (2019). Beyond depression: Other uses for tricyclic antidepressants. *Cleveland Clinic Journal of Medicine*, 86(12), 807-814.

Silberstein, S. D. (2009). Preventive migraine treatment. *Neurologic clinics*, 27(2), 429-443.

Silberstein, S. D. (2015). Preventive migraine treatment. *Continuum: Lifelong Learning in Neurology*, 21(4 Headache), 973.

Thour, A., & Marwaha, R. (2019). Amitriptyline.

Tripathi, G. M., Kalita, J., & Misra, U. K. (2018). A study of oxidative stress in migraine with special reference to prophylactic therapy. *International Journal of Neuroscience*, 128(4), 318-324.

Torraco, R. J. (2005). Writing integrative literature reviews: Guidelines and examples. *Human resource development review*, 4(3), 356-367.

Torraco, R. J. (2016). Writing integrative reviews of the literature: Methods and purposes. *International Journal of Adult Vocational Education and Technology (IJAVET)*, 7(3), 62-70.

Von Brevern, M., & Lempert, T. (2020, February). Vestibular migraine: treatment and prognosis. In *Seminars in Neurology* (Vol. 40, No. 01, pp. 083-086). Thieme Medical Publishers.

Whittemore, R., & Knafl, K. (2005). The integrative review: updated methodology. *Journal of advanced nursing*, 52(5), 546-553.