e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2023; 13(11); 11-18

Original Research Article

An Observational Study to Evaluate the Efficacy and Tolerability of Sodium Valproate and Amitriptyline in Migraine Prevention

Balram Sai Prasanna

Postgraduate, Department of Pharmacology, Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar, Telangana.

Received: 30-09-2023 / Revised: 14-10-2023 / Accepted: 07-11-2023
Corresponding Author: Balram Sai Prasanna
Conflict of interest: Nil

Abstract

Background: Migraine headaches are a recurring condition marked by intense and throbbing pain, typically localized to one side of the head. These headaches are frequently accompanied by symptoms like nausea, vomiting, and heightened sensitivity to light and sound. Typically, they persist for a duration ranging from four hours to three days. The current study was conducted to investigate the efficacy and tolerability of sodium valproate versus Amitriptyline in migraine prophylaxis

Methods: Patients were included in the study based on predefined inclusion and exclusion criteria. We collected data from 90 outpatient department (OPD) prescription sheets of individuals with migraine who were undergoing prophylactic therapy with either amitriptyline or sodium valproate in the Neurology Department. A record of the patient's baseline characteristics was maintained in a case record form. Other data collected included the duration of symptoms, frequency of headaches, results of neurological examinations, as well as assessments of migraine pain severity and functional disability.

Results: After 3 months, sodium valproate outperformed amitriptyline with a significantly higher percentage of patients experiencing >50% improvement in VAS score (68.29% vs. 50.00%, P = 0.012). The trend continued at 6 months, with sodium valproate surpassing amitriptyline in VAS score improvement (95.12% vs. 71.43%, P = 0.021). In terms of headache severity, a greater proportion of sodium valproate patients had ≥ 1-grade improvement at 3 months (90.24% vs. 76.19%, P = 0.047). Additionally, functional disability improvement was significantly higher for sodium valproate at 3 months (97.56% vs. 90.47%, P = 0.031). Overall, sodium valproate proved more effective in alleviating pain and improving headache and functional disability in migraine patients. Among 83 migraine subjects, 19 in the amitriptyline group and 22 in the sodium valproate group experienced adverse drug reactions.

Conclusion: Sodium valproate outperforms amitriptyline in improving pain severity, headache intensity, and functional disability in migraine patients. These findings align with earlier research outcomes. Sedation and weight gain were the most common ADRs associated with both medications. Amitriptyline exhibited a higher incidence of ADRs among patients, particularly after the 6-month mark. The results of this investigation indicate that, for individuals with migraines, sodium valproate may represent a preferable choice over amitriptyline.

Keywords: Amitriptyline, Sodium Valproate, Migraine, Efficacy, ADRs

Introduction

Migraine, a prevalent and debilitating neurological disorder, affects both men and women equally. Research from population-based studies suggests that approximately 10-12% of the general population experiences migraine. [1-3] This condition ranks as the third most widespread disorder and the seventh leading specific cause of disability worldwide. [4] It's considered a disabling illness because it primarily afflicts individuals between the ages of 22 and 55, a crucial period representing the peak of our productive years. Migraine significantly impacts the quality of life, often causing individuals to forgo sports, social events, or holidays to avoid painful migraine episodes. [5] Those with migraines are also at risk of developing depression and anxiety, due to the illness's pattern and the associated economic burden. [6] William Gower noted that migraine and epilepsy can coexist in the same individual, making migraine a "border-land" of epilepsy and potentially exacerbating epileptic seizures. [7] Consequently, the management of migraines is a crucial healthcare concern. [8] Migraine management remains challenging, involving both pharmacological and non-pharmacological approaches. Non-pharmacological management entails behavioral and lifestyle changes, such as avoiding triggering

factors, providing assurance, and regular patient follow-up. This also includes steering clear of foods that may provoke migraine attacks, like cheese, fermented products, hot dogs, and fatty foods. Exercise programs are often recommended, while those under stress may benefit from effective stress management to reduce the frequency of migraine attacks. [9] Migraine treatment options encompass both preventive (prophylactic) and abortive (symptomatic) approaches. Symptomatic treatment ranges from simple analgesics like non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen to more specialized options like triptans or the less commonly used dihydroergotamine. However, when dealing with frequently recurring, severe, disabling, and prolonged migraine attacks, long-term prophylaxis becomes necessary.

Prophylaxis involves daily administration of anti-migraine compounds, regardless of the recurrence of migraine attacks. [10] The therapeutic options for migraine prophylaxis include beta-blockers, calcium-channel blockers, partial serotonin agonists, tricyclic antidepressants (e.g., Amitriptyline), and anti-epileptics like gabapentin, valproate, and topiramate. [11-13] All these drugs have demonstrated efficacy in migraine prophylaxis, but they also come with relevant adverse effects, contraindications, and potential interactions with other concurrent medical conditions and treatments. Among the wide variety of available drugs, Amitriptyline and Sodium valproate are the two most common options for prophylactic therapy, both having a Class 1 recommendation for migraine prophylaxis. However, there is a limited number of studies comparing the efficacy and safety profiles of these two medications. Thus, it is essential to investigate the efficacy and tolerability of sodium valproate versus Amitriptyline in migraine prophylaxis to determine the optimal treatment option between them in this study.

Material and Methods

This study was a Prospective observational study conducted in the Department of Neurology along with the Department of Pharmacology, Kakatiya Medical College and MGM Hospital, Warangal. Institutional Ethical approval was obtained for the study. Written consent was obtained from all the participants of the study after explaining the nature of the study in the vernacular language. Those voluntarily willing to participate were only included.

Inclusion Criteria

1. Patients diagnosed with migraine as per established criteria by the International Headache Society.
2. Aged 18 and above
3. Having more than 4 migraine attacks per month
4. Those prescribed with sodium valproate or amitriptyline medications
5. Those willing to participate in the study and available for follow-up

Exclusion Criteria

1. Patients with a history of drug allergy especially to sodium valproate and amitriptyline.
2. History of hypertension and cardiovascular diseases
3. Patients with glaucoma, papilloedema, and epilepsy
4. Those not available for follow-up appointments

Patients were included in the study based on predefined inclusion and exclusion criteria. We collected data from 90 outpatient department (OPD) prescription sheets of individuals with migraine who were undergoing prophylactic therapy with either amitriptyline or sodium valproate in the Neurology Department. A record of the patient's baseline characteristics was maintained in a case record form. Other data collected included the duration of symptoms, frequency of headaches, results of neurological examinations, as well as assessments of migraine pain severity and functional disability. These assessments were conducted both before and after the treatment, using the Visual Analog Scale (VAS) score and the Migraine Disability Assessment (MIDAS) score, respectively. To gauge the efficacy of the treatments, we monitored the reduction in the number of migraine attacks per month, the severity of pain, and the level of functional disability relative to the baseline at the end of the 3-month and 6-month treatment periods. Any adverse drug reactions were meticulously documented using the Adverse Drug Reaction (ADR) form, and their causal relationship was assessed using the World Health Organization (WHO) Causality Assessment Scale.

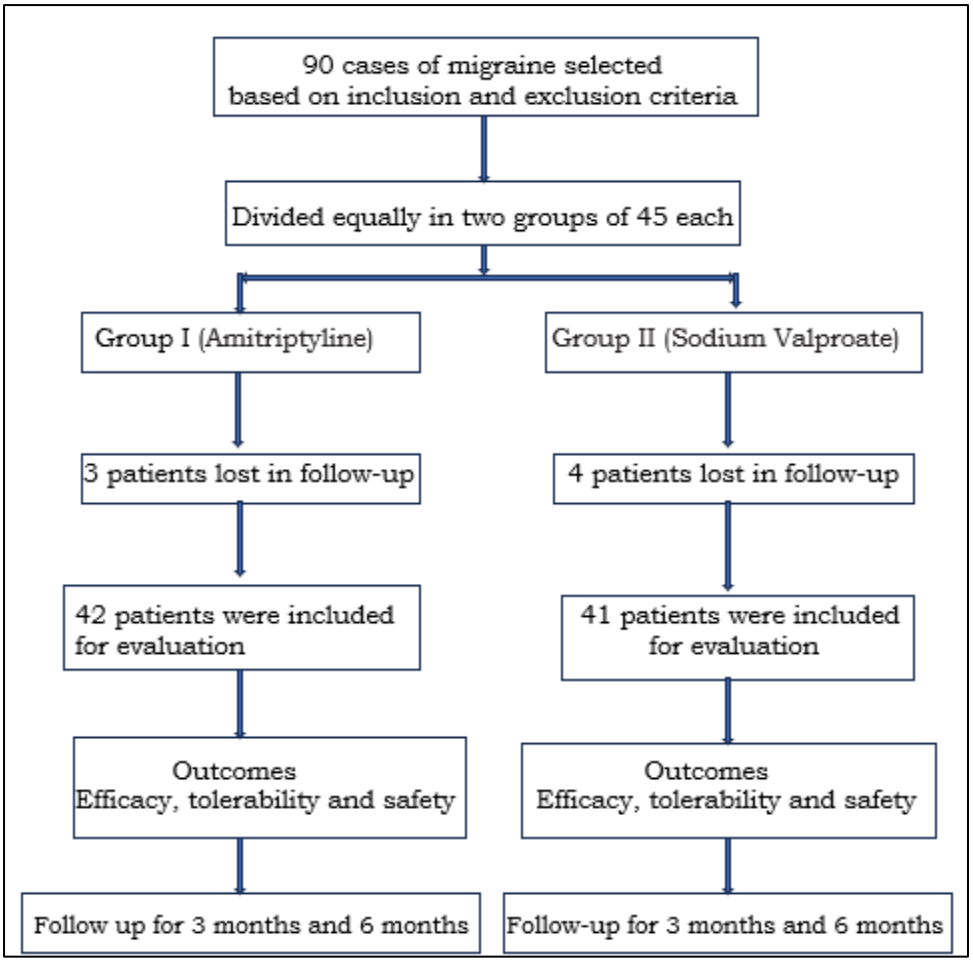

Figure 1: **Showing the blueprint of the study**

Effectiveness: The primary effectiveness endpoints were defined as achieving the following criteria: a reduction in headache frequency by more than 50%, an improvement of at least one grade in migraine disability, and a pain score on the Visual Analog Scale (VAS) that improved by more than 50%. These assessments were made by comparing the baseline measurements with those at 3 months and 6 months of treatment.

Tolerance and Safety: Patient tolerability and safety were continuously assessed by monitoring adverse events. Tolerability evaluations included tracking the occurrence of adverse events, instances of participants prematurely discontinuing the study due to undesirable side effects, and the reporting of any serious adverse events.

Statistical analysis: The data gathered during the study were entered into a Microsoft Excel spreadsheet and subsequently subjected to analysis. Continuous variables for the amitriptyline and sodium valproate groups were presented as mean standard deviation, percentages, and frequencies. Categorical variables to compare the severity of pain, headache frequency, and functional disability at baseline, 3 months, and 6 months within each group, analysis of variance (ANOVA) was employed. The number of patients meeting the primary and secondary endpoints at the 3-month and 6-month time points was compared using the chi-square test. Significance was attributed to variables when the two-tailed P-value was less than 0.05.

Results

Table 1 shows the age distribution of patients receiving amitriptyline (AMT) and sodium valproate (SV) for the treatment of migraine. The majority of patients in both groups are between the ages of 21 and 40, with a slightly higher percentage of patients in the sodium valproate group (73.17%) than in the amitriptyline group (73.80%). There are also slightly more patients in the sodium valproate group in the 41-60 and 61-70 age groups (17.07% and 4.87%, respectively) compared to the amitriptyline group (14.29% and 4.76%, respectively). Overall, the age distribution of patients receiving amitriptyline and sodium valproate for migraine is similar.

Table 1: Age distribution of patients receiving Amitriptyline (Group I) and Sodium valproate (Group II)

Age	Group I (Amitriptyline)		Group II (Sodium valproate)	
	Frequency	Percentage	Frequency	Percentage
18 – 20	3	7.14	2	4.87
21 – 40	31	73.80	30	73.17
41 – 60	6	14.29	7	17.07
61 – 70	2	4.76	2	4.87
Total	42	100	41	100

The majority of patients receiving amitriptyline and sodium valproate for migraine are between the ages of 21 and 40. This suggests that these medications are most commonly used to treat migraine in younger adults. There are slightly more patients in the sodium valproate group in the 41-60 and 61-70 age groups. This may be due to the fact that sodium valproate is also used to treat other conditions, such as epilepsy and bipolar disorder, which are more common in older adults. Overall, the age distribution of patients receiving amitriptyline and sodium valproate for migraine is similar.

Out of the 42 cases in group I males were 14 (33.33%) and females were 28 (66.67%). Similarly, for group II out of 41 cases, males were 15 (36.58%) and females were 26(63.41%). The frequency of migraine was higher in females in this cohort consequently the usage of both drugs was more in female cases as compared to males. The participants in the study experienced migraine symptoms for a duration ranging from 1 to 6 years, and the number of headache attacks they encountered each month fell within the range of 4 to 12.

Table 2: Classification of patients according to migraine-induced disability as determined by the MIDAS score. [14]

		Pretreatment		Post-treatment 3 months		
Group	Grade	Frequency	Percentage	Frequency	Percentage	P value
Group I Amitriptyline	I	0	00.00	15	35.71	0.0125*
	II	32	76.19	18	42.85	
	III	9	21.43	9	21.43	
	IV	1	2.38	00	00.00	
Total		42	100	42	100	
Group II Sodium Valproate	I	0	00.00	12	29.27	0.0256*
	II	9	21.95	19	46.34	
	III	22	53.66	9	21.95	
	IV	10	24.39	1	2.44	
Total		41	100	41	100	

* Significant

Table 2 shows the classification of patients according to migraine-induced disability as determined by the MIDAS score (before treatment). The MIDAS score is a questionnaire that is used to assess the impact of migraines on a person's daily life. MIDAS grade I (scores 0 – 5) grade II mild disability (Score 6 – 10), grade III moderate disability (Score 11 – 20) and grade IV (Score 21+) severe disability. The higher the MIDAS score, the more severe the disability. There is a significant difference in migraine-induced disability between patients in Group I (amitriptyline) and Group II (sodium valproate). In Group I, 76.19% of patients had a MIDAS score of II, indicating moderate disability. In Group II, only 21.95% of patients had a MIDAS score of II, indicating that sodium valproate was more effective at reducing migraine-induced disability. There is a significant difference in the number of patients in each group with a MIDAS score of IV, indicating severe disability. In Group I, only 2.38% of patients had a MIDAS score of IV, while in Group II, 24.39% of patients had a MIDAS score of IV. This suggests that sodium valproate is also more effective at preventing severe migraine-induced disability. After 3 months, more than 50% improvement in overall headache frequency was observed in 78.57% of patients in the amitriptyline group and 82.92% of patients in the sodium valproate group. Overall, it was found that sodium valproate is more effective than amitriptyline at reducing migraine-induced disability, including severe disability.

Table 3: Assessment of pain severity before treatment using the VAS score distribution.

Group	Grade	Frequency	Percentage	P value
Group I Amitriptyline	5	1	2.38	0.0125*
	6	10	23.81	
	7	21	50.00	
	8	6	14.28	
	9	4	9.52	
Total		42	100	
Group II Sodium Valproate	6	1	2.44	0.0256*
	7	25	60.97	
	8	12	29.27	
	9	2	4.88	
	10	1	2.44	
Total		41	100	

Table 3 shows the distribution of VAS scores (Visual Analogue Scale scores) for pain severity before treatment in patients randomized to receive either amitriptyline or sodium valproate for migraine prophylaxis. The VAS score is a 10-point scale used to measure pain intensity, with 0 representing no pain and 10 representing the worst possible pain. The majority of patients in both groups had moderate pain (VAS score of 7) before treatment. However, there was a significantly higher proportion of patients in the amitriptyline group with severe pain (VAS score of 9 or 10) compared to the sodium valproate group (9.52% vs. 4.88%). In the amitriptyline group, the most common VAS score was 7 (50.00%), followed by 5(23.81%), 6(14.28%), and 9(9.52%). This suggests that the majority of patients in the amitriptyline group had moderate to severe pain prior to treatment. In the sodium valproate group, the most common VAS score was 7 (60.97%), followed by 8 (29.27%), 6 (2.44%), and 9 (4.88%). This suggests that the majority of patients in the sodium valproate group had moderate pain prior to treatment, and there were fewer patients with severe pain. The difference in the proportion of patients with severe pain between the two groups was statistically significant (P = 0.0256). This suggests that sodium valproate is more effective at reducing pain severity in patients with migraine.

Table 4: Improvement in VAS score, Severity of headache, and Functional disability at the end of 3 months and 6 months

Group		Improvement (%)	Group I Amitriptyline	Group II Sodium Valproate	P value
VAS Score	At the end of 3 months	> 50	21 (50.00%)	28 (68.29%)	0.012*
		< 50	21 (50.00%)	13 (31.71%)	
	At the end of 6 months	> 50	30 (71.43%)	39 (95.12%)	0.021*
		< 50	11 (26.19%)	2 (4.87%)	
Severity of Headache improvement ≥ 1 grade improvement	At the end of 3 months	Improved	32 (76.19%)	37 (90.24%)	0.047
	At the end of 6 months	Not improved	9(21.43%)	4(9.75%)	
Functional disability ≥ 1 grade improvement	At the end of 3 months	Improved	38 (90.47%)	40 (97.56%)	0.031*
	At the end of 6 months	Not improved	4(9.52%)	1(2.43%)	

Table 4 shows the improvement in VAS score, severity of headache, and functional disability at the end of 3 months and 6 months in patients with migraines randomized to receive either amitriptyline or sodium valproate.

VAS Score: At the end of 3 months, a significantly higher proportion of patients in the sodium valproate group had a >50% improvement in VAS score compared to the amitriptyline group (68.29% vs. 50.00%, P = 0.012). At the end of 6 months, a significantly higher proportion of patients in the sodium valproate group had a >50% improvement in VAS score compared to the amitriptyline group (95.12% vs. 71.43%, P = 0.021).

Severity of Headache: At the end of 3 months, a higher proportion of patients in the sodium valproate group had a ≥ 1 grade improvement in headache severity compared to the amitriptyline group (90.24% vs. 76.19%, P = 0.047). At the end of 6 months, a higher proportion of patients in the sodium valproate group had a ≥ 1-grade improvement in headache severity compared to the amitriptyline group (97.56% vs. 71.43%, P = 0.031).

Functional Disability: At the end of 3 months, a significantly higher proportion of patients in the sodium valproate group had a ≥ 1-grade improvement in functional disability compared to the amitriptyline group (97.56% vs. 90.47%, P = 0.031). At the end of 6 months, a significantly higher proportion of patients in the sodium valproate group had a ≥ 1-grade improvement in functional disability compared to the amitriptyline group (97.56% vs. 95.24%, P = 0.047). Overall, sodium valproate was more effective than amitriptyline at improving pain severity, headache severity, and functional disability in patients with migraine. Out of a total of 83 migraine subjects, 19 patients in the Amitriptyline group had developed ADR, whereas, in the sodium valproate group, 22 patients developed ADR during the study period.

Table 5: Improvement in VAS score, Severity of headache, and Functional disability at the end of 3 months and 6 months

Adverse Drug Reaction	Group I (Amitriptyline)	
	3-months	6-months
Rash	1(2.3%)	1 (2.3%)
GI upset	2 (4.7%)	0 (0.00)
Dry mouth	1 (2.3%)	3 (7.14%)
Menstrual irregularities	4 (9.5%)	3 (7.14%)
Weight gain	2 (4.7%)	9 (21.43%)
Sedation	18(42.85%)	19(45.24%)
Total	28(66.67%)	35(83.33%)
	Group II (Sodium Valproate)	
Weight gain	8 (19.51%)	9 (21.95%)
GI upset	2 (4.87%)	1 (2.44%)
Mood changes	3 (7.31%)	2 (4.8%)
Menstrual irregularities	7 (17.07%)	3 (7.31%)
Acne	4 (9.70%)	3 (7.31%)
Sedation	4 (9.70%)	8 (19.5%)
Total	28 (68.29%)	26 (63.4%)

The table shows the incidence of adverse drug reactions (ADRs) in patients with migraine who were treated with either amitriptyline or sodium valproate for 3 and 6 months.

Amitriptyline: The most common ADRs at 3 months were sedation (42.85%) and dry mouth (2.3%). The most common ADRs at 6 months were sedation (45.24%) and weight gain (21.43%). The proportion of patients with ADRs increased from 66.67% at 3 months to 83.33% at 6 months.

Sodium valproate: The most common ADRs at 3 months were weight gain (19.51%) and menstrual irregularities (17.07%). The most common ADRs at 6 months were weight gain (21.95%) and sedation (19.5%). The proportion of patients with ADRs decreased slightly from 68.29% at 3 months to 63.4% at 6 months. The table shows that both amitriptyline and sodium valproate can cause a variety of ADRs in patients with migraine. The most common ADRs for both medications were sedation and weight gain. However, amitriptyline was associated with a higher proportion of patients with ADRs overall, especially at 6 months.

Discussion

The results from this prospective observational study on migraine prophylaxis indicate that both Amitriptyline and Sodium valproate significantly improved migraine symptoms and reduced the frequency and duration of migraine attacks. The prevalence of Amitriptyline (AMT) and Sodium valproate (SV) usage was higher among females (AMT= 35 66.67%) and SV = 34 (63.41%), consistent with previous research. [1, 15] This increased susceptibility to migraine among females, particularly during their active reproductive years due to hormonal changes, is prominent during this period, possibly influenced by genetics (male to female ratio 1:3). [16] The most common age group receiving these drugs ranged from 21 to 40 years (88% in the AMT group and 87.5% in the SV group), aligning with findings from studies like those conducted by Bigel M et al. [17]. Migraine is prevalent in this age group due to exposure to various triggering factors such as stress, hormonal imbalances, high-fat diets, fasting, nutritional deficiencies, sunlight exposure, and more. Overall, there was a notable improvement in headache

frequency, migraine disability, and VAS pain scores when comparing baseline data with the 3-month and 6-month treatment outcomes for both drugs.

Upon concluding the 3-month assessment, the Sodium valproate group displayed a notable reduction in pain severity, with 70% of patients (p-value <0.012) experiencing this improvement. Moreover, 68.29% of patients (p-value <0.021) in the Sodium valproate group showed more than a 50% decrease in headache frequency and at least a one-grade functional disability improvement compared to the Amitriptyline group. This observation aligns with a comparative study on migraine prophylaxis conducted by J. Kalita et al. [1] These findings suggest that sodium valproate is a more effective treatment for migraine than amitriptyline. This is likely due to the different mechanisms of action of the two medications. Sodium valproate is thought to work by increasing the levels of GABA, a neurotransmitter that has inhibitory effects on the brain. Amitriptyline is thought to work by increasing the levels of serotonin and norepinephrine, two neurotransmitters that are involved in pain regulation.

At the 6-month mark, a substantial difference in response between the two treatment options became evident. Sodium valproate demonstrated better efficacy, which contrasted with the findings of the study by J. Kalita et al. [1] where no significant difference was observed between the two options in terms of VAS scores and other outcome parameters. The variation between our study and the one by J. Kalita et al. [1] could be attributed to genetic variances, pharmaceutical differences, and disparities in dosing schedules. In our study, Amitriptyline and Sodium valproate were prescribed within a dose range of 10-25 mg/day and 200-400 mg/day, respectively, while in their study, the dose range was higher, with Amitriptyline and Sodium valproate ranging from 25-50 mg/day and 200-1000 mg/day, respectively. Our study not only focused on headache frequency and pain severity as primary endpoints but also assessed tolerability, including the incidence of adverse events, premature withdrawal due to side effects, and serious adverse events. This comprehensive approach sets our study apart from previous ones. We also evaluated the causality of adverse drug reactions (ADRs) associated with both Amitriptyline and Sodium valproate using the WHO-UMC causality assessment scale, which allowed for a more detailed and thorough evaluation. When comparing the tolerability profiles of both drugs at 3 and 6 months out of 42 migraine patients in the Amitriptyline group, only 28 developed ADRs (Table 5). The most commonly reported ADR with Amitriptyline usage was sedation 18(42.85%), followed by menstrual irregularities (9.5%) and others as given in Table 5 at the end of 3 months.

Sedation and weight gain 45.24% and 21.43% respectively remained the most ADRs at the end of 6 months (Table 5) These findings were consistent with a study by Goncalves AL et al, and no serious adverse events were reported. In the Sodium valproate group, 28 patients experienced ADRs, among the 41 patients, 19.51% experienced weight gain, and 17.07% experienced menstrual irregularities. 9.70% experienced acne and sedation each and gastrointestinal upset at the end of 3 months. The weight gain was 21.95% and sedation at 19.5% remained the common ADRs in the sodium valproate group at the end of 6 months. These results were comparable to a study by T Mansoureh et al, and no hematological or hepatic side effects were observed in either group. In this study, the causality of ADRs associated with Amitriptyline and Sodium valproate was assessed using the WHO-UMC causality assessment scale, [18] and most ADRs in both groups had a probable causal association at both 3 and 6 months (AMT group at 76.5% 3 months and 68.5% at 6 months). Notably, previous studies did not evaluate the causality of ADRs associated with the use of migraine prophylactic drugs, and this assessment enhances the understanding of the relationship between drug exposure and adverse reactions. [19-21] The findings of this study suggest that sodium valproate may be a better choice than amitriptyline for patients with migraines who are concerned about ADRs. However, it is important to note that both medications can cause serious ADRs, and patients should be monitored closely by their doctor.

Conclusion

Sodium valproate proves to be more effective than amitriptyline in mitigating migraine-related disability, including severe cases. Additionally, sodium valproate outperforms amitriptyline in improving pain severity, headache intensity, and functional disability in migraine patients. These findings align with earlier research outcomes. Nevertheless, both amitriptyline and sodium valproate can lead to various adverse drug reactions (ADRs) in migraine patients. Sedation and weight gain were the most common ADRs associated with both medications. Notably, amitriptyline exhibited a higher incidence of ADRs among patients, particularly after the 6-month mark. The results of this investigation indicate that, for individuals with migraines, sodium valproate may represent a preferable choice over amitriptyline. It is essential to recognize that both drugs can result in ADRs, necessitating vigilant monitoring by healthcare professionals.

References

1. Kalita J, Bhoi SK, Misra UK. Amitriptyline vs divalproate in migraine prophylaxis: a

randomized controlled trial. Acta Neurol Scand 2013; 128: 65–72.
2. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders. Cephalalgia. (2nded) 2004; 24:9-1
3. Rizzoli P. Preventive pharmacotherapy in migraine. Headache. 2014; 54:364-9.
4. Steiner T.J., Stovner L.J., Jensen R. et al. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J Headache Pain 2020; 21: 137.
5. Krymchantowski A V, Bigal ME, Moreira PF. New and emerging prophylactic agents for migraine. CNS Drugs. 2002; 16:611-34.
6. Lionetto, Negro A, Palmisani S, Gentile G, Del Fiore MR, Mersieri M, et al. Emerging treatment for chronic migraine and Refractory chronic migraine. Expert opinion emerges drugs. 2012; 17:393-406.
7. Zandieh A, Khahaki ZZ, Sadegian H, Pourashraf M, parvis S et al. The underlying factor structure of National Institute of Health Stoke scale: An exploratory factor analysis. Int J Neurosci. 2013; 122:140-4.
8. Stewart W F, Lipton RB, Celentano DD, Reed ML; Prevalence of Migraine headache in the United States. Relation to age, income, race, and other socio-demographic factors. JAMA.1992; 267:64-69.
9. Varkey E, Cider A, Carlsson J, Linde M. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. Cephalalgia. 2011 Oct;31 (14):1428-38.
10. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: Data from the American migraine study II. Headache. 2001;41: 646-57.
11. Ghabaee M, Bayati A, Amri Saroukolaei S, Sahraian MA, Sanaati MH, Karimi P, Houshmand M, Sadeghian H, Hashemi Chelavi L. Analysis of HLA DR2&DQ6 (DRB1*1501, DQA1*0102, DQB1*0602) haplotypes in Iranian patients with multiple sclerosis. Cell Mol Neurobiol. 2009 Feb; 29 (1):109-14.
12. Andlin-Sobocki P. Jonsson B, Wittchen HU, Olesen J. Cost of disorders of the brain in Europe. Eur J Neurol. 2005;12:1-27.
13. Ghabaee M, Omranisikaroudi M, Amrisaroukolaei S, Meysamie A, Sahraian MA, Bayati A, Sanati MH, Houshman M, Sadeghian H, Vajihazaman K. Mitochondrial mutation in Iranian patients with multiple sclerosis, correlation between haplogroups H, A and clinical manifestations. Cell Mol Neurobiol. 2009; 29(3):341-6.
14. Stewart WF, Lipton RB, Kolodner KB, Sawyer J, Lee C, Liberman JN. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. Pain. 2000 Oct;88(1):41-52.
15. Amiri P, Kazeminasab S, Nejadghaderi SA, Mohammadinasab R, Pourfathi H, Araj-Khodaei M, Sullman MJM, Kolahi AA, Safari S. Migraine: A Review on Its History, Global Epidemiology, Risk Factors, and Comorbidities. Front Neurol. 2022 Feb 23;12:800605.
16. Vetvik KG and MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol .2017;16: 76–87.
17. Bigal ME, Liberman JN, Lipton RB. Age-dependent prevalence and clinical features of migraine. Neurology 2006 Jul 25;67(2): 246-51.
18. The use of the WHO-UMC system for standardized case causality assessment. PDF available from file:///D:/Download/whocausality-assessment.pdf [Accessed on Aug 28 , 2023]
19. D'Amico D, Tepper SJ. Prophylaxis of migraine: general principles and patient acceptance. Neuropsychiatr Dis Treat. 2008 Dec;4(6):1155-67.
20. Brandes JL, Kudrow DB, Rothrock JF, et al. Assessing the ability of topiramate to improve the daily activities of patients with migraine. Mayo Clin Proc. 2006;81(10): 13 11–9.
21. D'Amico D, Usai S, Grazzi L, et al. Quality of life and disability in primary chronic daily headaches. Neurol Sci. 2003;24:S97–S100.