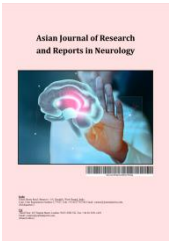

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Clinician's Perspectives and Prescription Practice of Sodium Valproate in the Management of Migraine, Bipolar Disorder, and Epilepsy in Indian Healthcare Settings

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Objective: To gather clinicians' perspectives on the management of neurological disorders such as migraine, bipolar disorder (BPD), and epilepsy, as well as the prescription practice of sodium valproate in Indian settings.
Methodology: This was a cross-sectional study carried out among clinicians specializing in migraine, BPD, and epilepsy management. The selected participants completed a 29-item questionnaire distributed via email or online platforms. The survey explored prescription practices,

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clinical observations, and preferences regarding sodium valproate and neurological disorder management. Data analysis involved descriptive statistics, with responses presented as frequencies and percentages.

Results: The survey involved 340 participants, and nearly half (45.88%) of them indicated that sodium valproate was their preferred choice for managing migraine, seizures, and BPD. Around 45% of the respondents noted that women are most frequently affected by migraine. Approximately 55% of the clinicians identified anxiety as the most common comorbid condition associated with migraine. About 47% of the participants preferred sodium valproate for migraine prophylaxis, while the majority (76.76%) of the clinicians chose it as the preferred treatment for BPD. Roughly 40% of the respondents reported that a daily dose of 300 mg of sodium valproate was commonly used for migraine. Approximately 54% of participants found that sodium valproate was most often prescribed to individuals in the 18-45 years age group. Additionally, 65% of the participants reported headaches or dizziness as common adverse effects of sodium valproate.

Conclusion: This study revealed that sodium valproate was a widely preferred treatment for migraine, epilepsy, and BPD among Indian clinicians, particularly for women and individuals aged 18-45 years. The findings highlighted the prevalent use of 300 mg daily dose for migraine and the common association of anxiety with migraine.

Keywords: BPD; epilepsy; migraine; seizures; sodium valproate.

1. INTRODUCTION

The burden of migraine, bipolar disorder, and seizures is significant, affecting millions worldwide. These conditions not only impair individuals' quality of life but also contribute to broader societal challenges, including economic costs and healthcare demands [1-3]. Migraine accounts for 4.9% of global ill health measured in years lived with disability (YLDs), impacting over 1 billion people, with India reporting the highest prevalence in 2019 at approximately 213,890,208 cases [4,5]. Globally, around 70 million people live with epilepsy, with nearly 12 million in India [6]. The World Mental Health survey estimates a global prevalence of BPD at 0.8%, with the incidence among adolescents and young adults increasing from 79.21 per 100,000 in 1990 to 84.97 per 100,000 in 2019 [7,8]. In India, a population-based study found current and lifetime prevalence rates of BPAD at 0.3% and 0.5%, respectively [8].

Sodium valproate (valproic acid), which belongs to the class of drugs known as anticonvulsants or antiepileptics, was approved by the Food and Drug Administration (FDA) for treating complex partial seizures, simple and complex absence seizures, and as an adjunctive therapy for multiple seizure types in both adults and pediatric patients. Sodium valproate inhibits voltage-gated sodium channels to reduce neuronal excitability and seizure activity. It also inhibits gamma-aminobutyric acid (GABA) transaminase, thereby boosting GABA levels and enhancing inhibitory effects. Additionally, sodium valproate promotes GABA synthesis by increasing glutamic acid decarboxylase activity and inhibits histone deacetylases (HDACs), influencing gene expression. Furthermore, sodium valproate modulates calcium channels, impacting neuronal signaling and pain pathways [9].

Understanding the prescription practice of sodium valproate was crucial for optimizing its use, improving patient outcomes, and enhancing neuronal health management. The present survey aims to collect expert opinions on the clinical application of sodium valproate maintenance therapy for migraine, epilepsy, and BPD within Indian healthcare settings.

2. MATERIALS AND METHODS

We carried out a cross-sectional, multiple-response questionnaire-based study involving clinicians with expertise in managing migraine, seizures, and BPD in the major Indian cities from June 2023 to December 2023.

2.1 Questionnaire

The questionnaire booklet named SCORE (Sodium Valproate Efficacy & Tolerability Profile) study was sent to the clinicians who were interested in participating in this study. The SCORE study questionnaire included 29 questions focusing on current prescription practices, clinical observations, and preferences related to sodium valproate, as well as experiences with migraine, epilepsy, and BPD in routine practice.

2.2 Participants

An invitation was sent to leading clinicians in treating migraine, epilepsy, and BPD in March 2023 for participation in this Indian survey. About 340 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provided necessary data. Participants were asked to complete the questionnaire without discussing it with their peers.

2.3 Statistical Methods

Descriptive statistics were employed for data analysis with categorical variables presented as percentages. The frequency of each variable and its corresponding percentage was calculated to illustrate its distribution. Graphs and pie charts were created using Microsoft Excel 2013 (version 16.0.13901.20400) to visually depict the distribution of categorical variables.

3. RESULTS

Out of 340 clinicians surveyed, nearly half (45.88%) of the respondents reported that sodium valproate was the preferred choice for migraine prophylaxis, seizures, and BPD (Table 1). Over half (52.65%) of the participants indicated that an average of 6-10 patients present with migraine headaches per day. Approximately 47% of the clinicians noted that fewer than 5 patients present with a history of seizures daily, and about 58% of the participants reported that fewer than 5 patients present daily with BPD. Approximately 45% of participants noted that women were most affected by migraine, while 43% of the clinicians observed that both genders equally experience migraine (Fig. 1) and about 55% of the participants identified anxiety as the most common comorbid condition in patients with migraine (Table 2).

Table 1. Distribution of response to the preferred use of sodium valproate in clinical disorders

Preference	Response rate (n = 340)
Migraine prophylaxis	9.41%
Seizures	19.71%
BPD	15.88%
All of the above	45.88%

Table 2. Distribution of response to most common comorbid condition noted in patients diagnosed with migraine

Common comorbid condition	Response rate (n = 340)
Anxiety	55.29%
Panic disorder	14.71%
Hypertension	10%
Diabetes	0.88%
Depression	11.76%
All of the above	7.35%

Approximately 27% of clinicians noted that men were most affected by BPD, while about 61% of respondents stated that the 18-35 age group was most affected by migraine. About 49% of participants indicated that the 36-50 age group was most affected by BPD. About 47% of experts preferred sodium valproate for migraine prevention, while 44% of participants preferred propranolol for the same purpose (Fig. 2), while nearly 77% selected it as the preferred treatment for BPD (Table 3).

Table 3. Distribution of response to preferred drug choice for patients with BPD

Preference	Response rate (n = 340)
Olanzapine	7.94%
Quetiapine	4.41%
Sodium valproate	76.76%
Lithium	9.12%
No preference	1.76%

Approximately 54% of participants reported that levetiracetam was the most effective antiepileptic based on its efficacy in seizures. Almost half (48.82%) of the respondents noted that 20-40% of patients were treated with sodium valproate for migraine prophylaxis, and about 43% reported the same proportion of patients receiving the drug as treatment for BPD. Nearly half (50.88%) of the clinicians indicated that 20-40% of patients were treated with sodium valproate for seizures. Approximately 40% of participants indicated that a daily dose of 300 mg of sodium valproate was commonly used for migraine, while 38% reported that the daily dose was 500 mg (Fig. 3). Approximately 48% of the clinicians stated that a daily dose of 500 mg was commonly used for BPD, and 56% recommended the same dosage for seizures. Nearly 54% of the participants found that the 18-45 age group was most prescribed with sodium valproate (Table 4).

Table 4. Distribution of response to common age group prescribed with sodium valproate

Age (years)	Response rate (n = 340)
<12	2.06%
12-18	11.76%
18- 45	54.12%
45-60	10.59%
>60	0.29%
All age groups	21.18%

Around 65% of the participants reported that fewer than 5% of patients experience osteoporosis (OP) or osteopenia as side effects of sodium valproate, with 31% observing these effects in patients aged 46-60 years. About 39% of the clinicians noted that OP or osteopenia typically develops after 12-24 months of treatment. Additionally, 65% of the participants reported headaches or dizziness as common adverse effects of sodium valproate (Fig. 4).

About 62% of the clinicians stated that brivaracetam has the advantage of lesser behavioral disturbances compared to sodium valproate, and more than half (58.24%) of the participants considered the flavor of sodium valproate syrup important for pediatric patients. Approximately 53% of the respondents found levetiracetam to be the most effective antiepileptic syrup based on its efficacy in seizures, and around 68% of the participants reported that levetiracetam injection was most effective for generalized tonic-clonic seizures. About 35% of the respondents indicated that 16-40% of individuals show improved outcomes with sodium valproate therapy for migraine, and 47% of the participants preferred dose escalation as the strategy for patients failing to respond to the initial sodium valproate treatment for migraine.

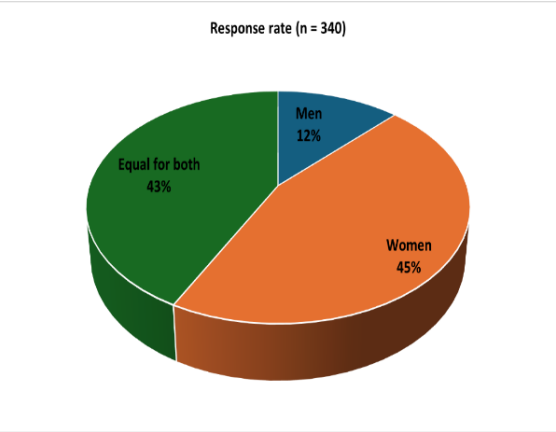

Fig. 1. Distribution of response to the predominant gender presenting with migraine headaches in clinical settings

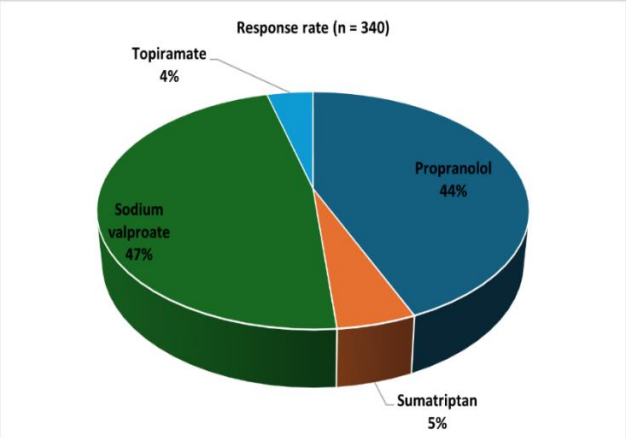

Fig. 2. Distribution of response to preferred drug choice for patients with migraine prophylaxis

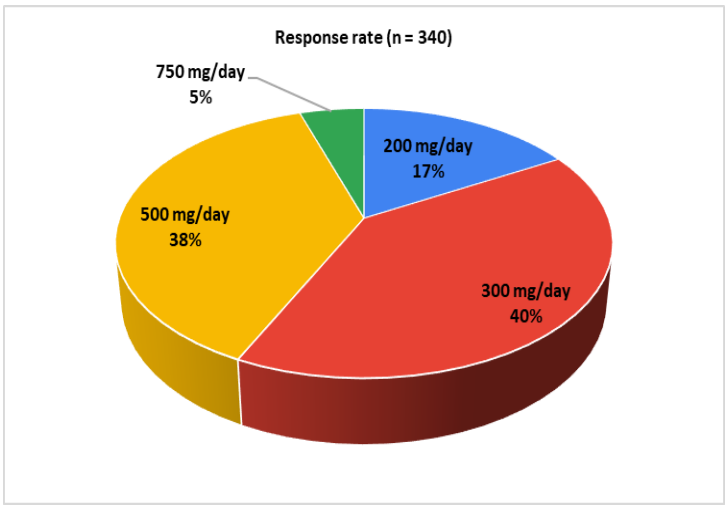

Fig. 3. Distribution of response to the daily dose of sodium valproate commonly used for migraine

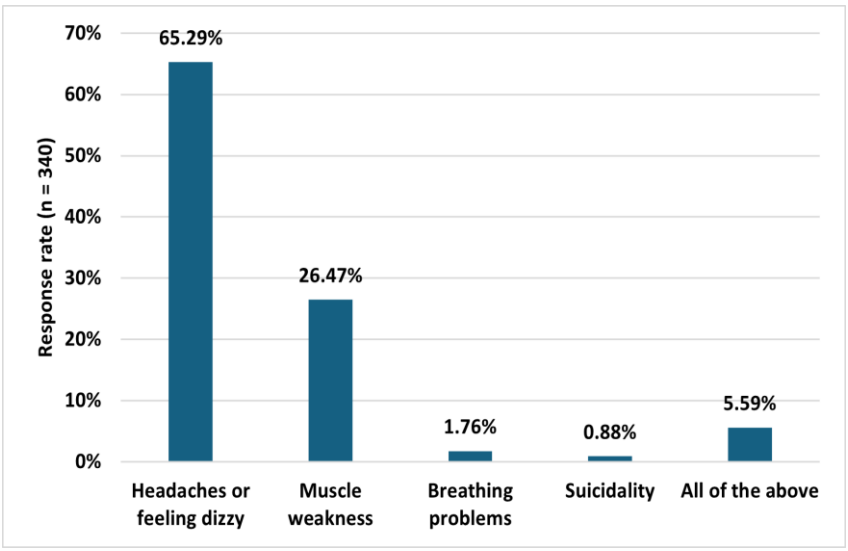

Fig. 4. Distribution of response to adverse effects reported with the use of sodium valproate

4. DISCUSSION

The survey indicated that sodium valproate was a widely preferred treatment for migraine, seizures, and BPD among clinicians in India, reflecting its established role in neurological disorder management. Vatzaki et al. highlighted that sodium valproate was widely used for migraine prophylaxis and was included in primary European guidelines [10]. Similarly, Silberstein et al. found that the drug was effective for migraine prevention, helping to reduce the frequency and severity of attacks [11]. In the realm of epilepsy, Marques et al. identified sodium valproate as the most effective antiepileptic drug for genetic generalized epilepsies [12]. Furthermore, Balagura et al. highlighted its broad spectrum of activity and diverse mechanisms of action, which have made it a first-line treatment for most seizure types in children for the past fifty years [13]. In the context of BPD, Roosen and Sienaert provided evidence supporting the use of sodium valproate for rapid cycling, while Charles L. Bowden affirmed its value as an effective treatment for BPD [14].

Many survey participants observed that women were more severely affected by migraine. Nappi et al. reported that migraine was more prevalent in women, with 17% of women meeting the diagnostic criteria for the condition. They also found that migraine frequency in women varies

with the menstrual cycle and pregnancy, and that combined hormonal contraception (CHC) or hormone replacement therapy (HRT) can either trigger or modify migraine [15]. Similarly, Kalkman et al. noted that migraine prevalence was two to three times higher in women compared to men [16]. Singh et al. described migraine as a common neurological disorder with a higher prevalence in women, marked by painful and debilitating headaches [17]. Kumar and Kadian found that the overall prevalence of migraine was estimated at 16%, with a sex prevalence ratio of 3:1, indicating a significantly higher frequency in women [18].

Most survey respondents identified anxiety as the most prevalent comorbid condition in patients with migraine. Cuciureanu et al. emphasized that anxiety was a frequent comorbidity associated with migraine, influencing disease prognosis, treatment, and clinical outcomes [19]. Senaratne et al. observed that symptoms of anxiety disorder were significantly more common in patients with migraine than those without [20]. Additionally, Jeyagurunathan et al. reported that anxiety and mood disorders were approximately two to ten times more prevalent among individuals with chronic migraine compared to the general population [21].

Many of the participants in the survey preferred sodium valproate for migraine prophylaxis, Kumar and Kadian noted that sodium valproate was used for migraine prophylaxis and was considered one of the first-line agents for migraine prevention [18]. Similarly, Vatzaki et al. reported that sodium valproate was commonly used to treat pre-chronic and chronic migraine [10].

The majority of the survey respondents identified sodium valproate as the preferred treatment for BPD. Chen et al. confirmed that sodium valproate was a commonly preferred medication for maintaining BPD [22]. Smith et al. concluded that sodium valproate effectively reduces depressive symptoms in acute bipolar depression and is well-tolerated [23]. Additionally, Zheng et al. highlighted that sodium valproate was widely used as an anticonvulsant for the maintenance treatment of BPD [24].

Many of the survey participants reported that a 300 mg daily dose of sodium valproate was commonly used for migraine. In line with this finding, Rahman et al. noted that the initial dosage of sodium valproate for migraine prophylaxis typically ranges from 250 to 500 mg, administered twice daily for one week [25]. Diener et al. reported that intravenous administration of sodium valproate, at doses of either 300 mg or 800 mg, was effective in treating acute migraine attacks [26]. Pascual et al. reported that the maintenance dose of sodium valproate typically ranges from 300 to 1000 mg daily [27].

Many of the participants stated that the 18-45 age group was most prescribed sodium valproate. In a study by Evans et al. conducted in England and Wales, it was reported that 87.7 out of every 1,000 individuals prescribed valproate were women or girls aged 14 to 45 years [28].

Most of the participants identified headaches and dizziness as common adverse effects of sodium valproate. Rahman et al. confirmed that dizziness and headaches were frequently associated with the drug [25]. Montalbano et al. reported additional common side effects including nausea, vomiting, constipation, increased appetite, weight gain, somnolence, and tremor [29]. Philip B. Bradley also noted that sodium valproate can cause dizziness, mild hypotension, and mild thrombocytopenia in some patients [30].

The major strengths of the survey include its large sample size and input from neurological disorder specialists regarding the effectiveness of sodium valproate. However, the results may be subject to bias due to reliance on expert opinion, and varying perspectives among clinicians could affect the findings. Additionally, the survey might not fully incorporate emerging evidence or evolving trends in the management of neurological disorders such as migraine, seizures, and BPD. It is crucial to acknowledge these limitations when interpreting the results and to recognize the need for further research to confirm the findings of the survey. Future studies could investigate the long-term effects of sodium valproate and explore strategies for improving patient education.

5. CONCLUSION

This study's findings highlight sodium valproate as the preferred treatment for managing neurological disorders such as migraine, BPD, and epilepsy, aligning with earlier studies that recognize its effectiveness and its status as a first-line treatment. The data indicate its prevalent use across various age groups, particularly in the 18-45 age range, with dosage preferences ranging from 300 mg to 500 mg daily.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

A written informed consent was obtained from each physician before initiation of the study.

ETHICAL APPROVAL

The study was conducted after getting approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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