



Original Research Article

Pharmaceutical chemistry for Novel drug discovery

Evaluation of Low Dose Divalproex Sodium in Night Terror in Adults – A Pilot Study in Indian Patients

Parthasarathy.S^{1*} and Ravi.S²

¹Professor, Department of Anesthesiology Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth. Puducherry, India

²Shree ENT care, ST multi-speciality hospital, kumbakonam. India

Abstract: Night terror is a form of parasomnias manifested as sudden arousal with cry and autonomic symptoms. It is commonly reported in children and reported to be rare in adults. There are no clear management strategies for the disease as the pathophysiology is unclear in adults. Studies about its management is limited in literature As Divalproex sodium is effective in parasomnias, we wished to try the same for this indication and find out its efficacy. We included 20 such adult patients with episodes at least twice a month, in a pilot study. All routine investigations, echocardiogram, MRI of the brain and electroencephalography (EEG) were normal in the patients. We started on Divalproex sodium (DIVALID – ER 250 mg- Linux laboratories) as a single dose in the night. The changes in symptomatology and side effects were noted. *Results:* The mean age was 34.45 ±8.98 years. The male: female ratio was 6:14. All the twenty patients became symptom free as soon as (within three to four days) the drug was started. There were no episodes in the next six months. The drug was stopped in 17 patients with no residual effects. One patient stopped on her own but it was uneventful. In two patients, it was continued as the patients were not very clear about complete recovery of symptoms even-though there were no such episodes. There were no distinct side effects. We conclude that a short six-month course of low dose of Divalproex sodium is effective in giving long term relief in adult patients with night terror.

Key words: parasomnias, night terror, Divalproex sodium

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***Corresponding Author**

Parthasarathy.S , Professor, Department of Anesthesiology Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth. Puducherry, India

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1. INTRODUCTION

Night terror, scientifically known as “pavor nocturnus”, is a type of parasomnia sleep disorder that is characterized by sudden wake up during a sleep with autonomic imbalance like sweating and gasping for air. A loss of consciousness may be elicitable for a few seconds. There may be loud vocalization or screaming with unintended walks. This may be followed by a disturbed sleep the same night. The episodes can recur every week or every fortnight. It is usually common in children. It is rare in adults¹. Most of the adult patients land up in cardiology clinic with a fear of an infarction². These patients without a diagnosis take polypharmacy with their side effects. The major difficulty in these disorders is lack of an investigation to confirm the diagnosis. As the diagnosis is one of exclusion it is difficult to diagnose and target with ideal drug. The disease is reported to be common in children but rare in adults. In adults, as the symptomology is vague and not under of the umbrella of any criteria, most of the patients are undiagnosed. Night terrors and somnambulism are parasomnias associated with non-REM sleep³. Paraxotine, benzodiazepines⁴ have been used in this disorder with variable success rates. As such, many adults are not symptomatic, they are prescribed drugs only to decrease self-injuries. The etiology of night terrors is presently not known. A few medical conditions such as obstructive sleep apnoea and restless leg syndrome are associated with the onset of this disorder⁵, the literature cannot truly delineate either the physiological or the psychological pathways which lead to this condition. Nightmares and most of the dreams are events arising from Rapid Eye Movement (REM) sleep, but night terrors do occur during Non-Rapid Eye Movement (NREM) sleep⁶. As there are lot of work done in night mares we wished to go into the details of nocturnal terrors especially in adults. Night terrors occur in adults that are similar to episodes described in children. Short, unpleasant dream like mentation⁷ may occur during sleep terrors episodes, possibly suggesting that an implication of complex mental activity taking place during slow wave sleep. Sleepwalking may actually be representing the acting out of the corresponding dreamlike mentation. While clearly distinct from sleep panic attacks, night terrors⁸ appear to occur in adults with histories of psychopathology. Hence targeting the psychopathology may be helpful in combating the disease. The initiation of benzodiazepines⁹ for the disease was suggested due to its proximity with the etiology of anxiety. Benzodiazepines alone may not treat the parasomnias and hence an alternative which targets the condition with improvement in sleep pattern is preferred. One such drug is divalproex sodium. It is an antiepileptic with calcium channel blocking activity. It has been used for many epileptic disorders and parasomnias. Very high doses may cause some side effects like disordered sleep and hair fall¹⁰. Hence, we decided a low dose of the drug as 250 mg in the night and assess its efficacy in the reduction of episodes. In the context of limited reports of night or nocturnal terrors in adults, the management guidelines are not studied. Divalproex sodium, even though well studied as antiepileptic, has so far not been used in adult nocturnal terrors. A very low dose especially in the night is unlikely to produce any distinct side effects¹¹. Hence, we went ahead with this initial preliminary feasibility study. The primary aim of the study is to evaluate the efficacy of low dose divalproex sodium in the reduction of symptoms. The secondary aims were to find out the sex predominance of the disorder and the incidence of side effects of the drug. The need for discontinuation of the drug was evaluated.

2. MATERIALS AND METHODS

This pilot study on night terror was conducted in a centre near Pondicherry of South India between April 2019 to March 2020. The study was approved by the institutional review board IRBSTH-104/2019 dated 10/03/2019. The first twenty willing adult patients by a convenient sampling method diagnosed to have nocturnal terror were included in the study. Being a pilot study, it is neither blinded nor randomized. The inclusion criteria were patients with typical symptomatology of sudden night arousal, sweats with a doubtful transient loss of consciousness. The symptoms should be occurring at least twice a month. An informed consent was taken about their inclusion in the study. All patients had ECG, echocardiogram, MRI brain and an EEG (on a non-episodic date) taken. All routine blood investigations were done. If all the investigations were normal, they were included. A mild hypertensive but well controlled were included. All patients with possible hypoglycaemia, or a history of wheezing, known epileptic, or on drugs which can alter central nervous system physiology for some other disease were excluded from the study. All children, pregnant and lactating mothers were excluded. Patients with obesity and with any possible suspicion of obstructive sleep apnoea were not included. Pulse and blood pressure were recorded in all positions and any evidence of autonomic dysfunction with orthostatic hypotension were excluded. Any history suggestive of childhood disease like the one described was elicited and such patients were not included. Informed consent was taken from each of the participants. A diary was maintained about their symptoms and side effect profile. Such twenty patients were started on Divalproex sodium (DIVALID – ER 250 mg- Linux laboratories) as a single dose in the night. All the patients were advised to take the tablet after food in the night preferably at 9 pm. All patients were advised to note any side effects and report to hospital in the event of any significant problems. All patients were reviewed after three months for effects and side effects. Again, the patients were advised to take the drug for a maximum period of six months. All patients were telephonically interviewed on and off to clear the doubts. The data were entered in an excel chart and subjected to simple descriptive analyses.

3. STATISTICAL ANALYSIS

As this being a pilot study, twenty patients who were willing to participate in the study were considered for the study. The drug is not used for this purpose so far and there is no earlier work on this concept. The study as such describes the effects and side effects of the drug for such disease and it is not controlled with an active or passive control. The patients' data were entered in excel sheets; transferred to SPSS 20.0 version and a simple descriptive analysis was done. The mean and the standard deviation along with simple expression of ratios were projected.

4. RESULTS

Nineteen out of the twenty patients completed the study. One patient took the drug for three months followed by self-stoppage due to absence of symptoms. The same patient was followed up for another three months to have no symptoms. The mean age of the study patients was 34.45 ± 8.98 years. The male: female ratio was 6:14. (Fig 1) All the patients had complete relief of symptoms. (Table 1)

| Table 1: Depicting the results in a nutshell | | |
|----------------------------------------------|----------------------------|--------------------|
| 1 | Age | 34.45 ± 8.98 years |
| 2 | Male : female ratio | 6:14 |
| 3 | Symptom relief : no relief | 20 : 0 |

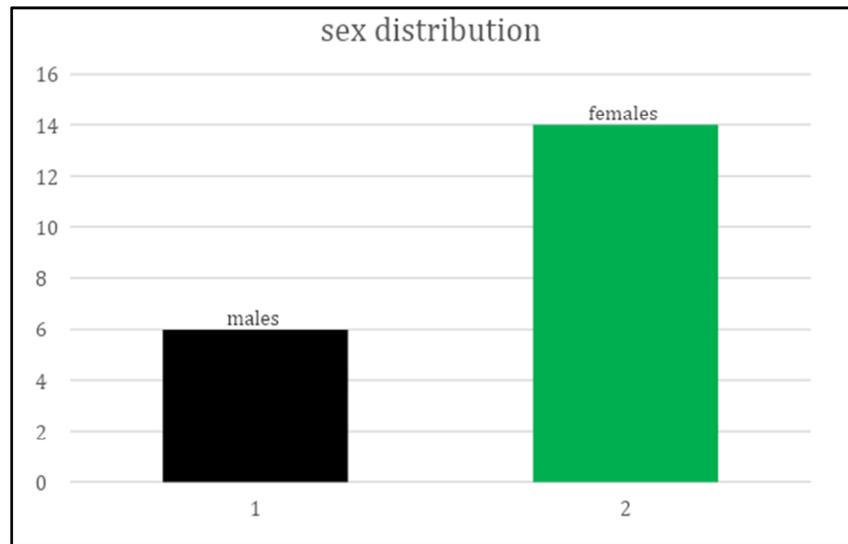


Fig 1 SHOWING SEX DISTRIBUTION

There was no such episode in the next three months. Drugs were continued and they were symptom free for six months in total. The drug was stopped at six months for seventeen patients and they were symptom free for the next two months. The rest two patients felt better with the drug but not very clear about complete recovery and wanted to continue for three more months. Two patients had sedation and difficulty in the early morning work for three to four days which subsided spontaneously on continuing the drug. One patient was a controlled hypertensive on amlodipine and never had a systolic blood pressure more than 140 mmHg any time during the study. All patients had no dreams and did not remember the next day. One patient noticed a transient hair fall but not very significant to warrant drug stoppage. The routine blood investigations were normal for all the patients after six months.

5. DISCUSSION

Nocturnal terrors or sleep terrors are characterized by sudden arousal a few hours after falling asleep usually with a cry or a loud sound. These are a variety of parasomnias during NREM sleep that affect approximately 5% of adults. There are a few studies which quote that is more common in males, but we have found out to be more common in women. These types of parasomnias are relatively rare in adults but we have found the incidence to be not uncommon¹². The major limitation to underline these incidence differences may be due to a lack of exact definition of the disorder. We had our cases with a cry and arousal but more with sweating panic: there was no significant loss of consciousness. It's many times difficult to elicit history from relatives about the questionable loss of consciousness as these episodes seem to be extremely transient. Electroencephalography and MRI brain were normal in our patients as it is difficult to take investigations during and just immediate to the attack. A continuous polysomnography could have thrown more light on our findings. We had all our

patients evaluated for a cardiac cause with an ECG and echocardiogram which were normal. But we did not resort to Holter monitoring as it was not advised. The second factor was the tremendous relief with the initiation of the drug which made the patients/clinicians think away from a cardiac cause. A variety of non-pharmacological methods¹³ have been tried for this condition with variable success. But we switched to drugs for ease and effectiveness. Cooper et al¹⁴ have used a combination of imipramine and diazepam for this disease, yet only in two cases. We have used a single drug with satisfactory results. Benzodiazepines and selective serotonin uptake inhibitors have been described for this entity with different results¹⁵. We resorted to valproate group as the disorder is supposed to be variant parasomnia and the drug is likely to act better in such condition¹⁶. As all the patients had an adult onset with abnormal arousal pattern without any dystonic features the probability of an epileptic attack was ruled out. It's very difficult to differentiate both but we had a normal EEG and clinical correlation to a seizure was not present. Video recordings of the episode may be more informative in doubtful cases but it needs hospitalisation and the procedure is cumbersome. Even though our cases got up with cry, screams and sweating, there was no sleep walking as told by either the patient or the attendee. In this pilot study, there were neither dreams nor remembrance, it's unlikely to be nightmares¹⁷. Usually it has been studied that co sleeping in childhood times decreased the incidence of sleep terrors; such history was not possible to elicit in this study.¹⁸ Hwang et al¹⁹ reported that tinnitus is associated with night terrors in adults which was not found in our cases. Choudhry et al²⁰ have stated that sleep terrors can occur in adults but more common in children and it is form of parasomnias. Hence, we idealized to target the disease with divalproex sodium. Its near ideal to video-monitor all the sleep patterns of the patient to register the movements and the level of consciousness. Our patients were not willing for the same.²¹ We did not measure stress levels by any scoring system before and after the drug²². We

did not encounter any major side effects except initial sedation in a few cases.

6. CONCLUSION

Sleep terror is classified as a type of parasomnias which is an undesirable behaviour or experience during sleep. Even though a lot of literature is found in children, only a few are available in adults. As the drug divalproex sodium is found to be effective in parasomnias, we tried in adult nocturnal terror. A single low dose divalproex sodium 250 mg in the night for a short period of six months is effective in adult patients with night terror. There was complete relief of symptoms in all the cases. There were no major side effects

9. REFERENCES

1. Kales JD, Kales A, Soldatos CR, Caldwell AB, Charney DS, Martin ED. Night Terrors: Clinical Characteristics and Personality Patterns. *Arch Gen Psychiatry*. 1980;37(12):1413–1417. doi:10.1001/archpsyc.1980.01780250099012.
2. Oudiette D, Leu S, Pottier M, et al. Dreamlike mentations during sleepwalking and sleep terrors in adults. *Sleep*. 2009;32(12):1621–1627.
3. Markov D, Jaffe F, Doghramji K. Update on parasomnias: a review for psychiatric practice. *Psychiatry (Edgmont)*. 2006;3(7):69–76.
4. Frölich Alfred Wiater Gerd Lehmkuhl J. Successful treatment of severe parasomnias with paroxetine in a 12-year-old boy. *Int J Psychiatry Clin Pract*. 2001;5(3):215–8. doi: 10.1080/136515001317021707. PMID: 24926757.
5. Patterson JF. Non-rapid-eye-movement parasomnia with behavior disorder. *South Med J*. 1989 Jun; 82(6):802.
6. Howard P, Twycross R, Shuster J, Mihalyo M, Rémi J, Wilcock A. Anti-epileptic drugs. *Journal of pain and symptom management*. 2011 Nov 1;42(5):788–804. doi: 10.1016/j.jpainsymman.2011.10.007.
7. Delphine Oudiette, MSc, Smaranda Leu, MD, Michel Pottier, MD, Marie-Annick Buzare, MD, Agnès Brion, MD, Isabelle Arnulf, MD, PhD, Dreamlike Mentations During Sleepwalking and Sleep Terrors in Adults, *Sleep*, 2009; 32, (12), , Pages 1621–1627 <https://doi.org/10.1093/sleep/32.12.1621>
8. Llorente MD, Currier MB, Norman SE, Mellman TA. Night terrors in adults: phenomenology and relationship to psychopathology. *J Clin Psychiatry*. 1992 Nov;53(11):392–4. PMID: 1459969
9. Waltman SH, Shearer D, Moore BA. Management of post-traumatic nightmares: a review of pharmacologic and nonpharmacologic treatments since 2013. *Current psychiatry reports*. 2018 Dec 1;20(12):108. doi:10.1007/s11920-018-0971-2.
10. Dreifuss FE, Langer DH. Side effects of valproate. *Am J Med*. 1988 Jan 25;84(1A):34–41. doi: 10.1016/0002-9343(88)90055-1. PMID: 3146224.
11. Schwartz TL, Massa JL, Gupta S, Al-Samarrai S, Devitt P, Masand PS. Divalproex Sodium Versus Valproic Acid in Hospital Treatment of Psychotic Disorders. *Prim Care Companion J Clin Psychiatry*. 2000;2(2):45–48. doi:10.4088/pcc.v02n0203

to discontinue the drug during the course of study of six months. A randomized controlled trial comparing established drugs is warranted.

7. AUTHORS CONTRIBUTION STATEMENT

Dr S.Ravi has devised the concept, data collection, Dr S. Parthasarathy has done the write up, supervision and communication.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

12. Paolo Tinuper, Francesca Bisulli, and Federica Provini, The parasomnias: Mechanisms and treatment. *Epilepsia*, 2012; 53(Suppl. 7):12–19. doi: 10.1111/j.1528-1167.2012.03710.x.
13. Maria Ntafouli, Andrea Galbiati, Mary Gazea, Claudio L.A. Bassetti & Panagiotis Bargiotas (2020) Update on nonpharmacological interventions in parasomnias, *Postgraduate Medicine*, 132:1, 72–79, DOI: 10.1080/00325481.2019.1697119.
14. Cooper, A. I. Treatment of coexistent night-terrors and somnambulism in adults with imipramine and diazepam. *The Journal of Clinical Psychiatry*, 1987; 48(5), 209–210.
15. Children Sleep Clinic. Medication in sleep disorders—posted by Indonesian children. 2009 September 13. <https://sleepclinic.wordpress.com/2009/09/13/medicati-on-in-sleep-disorders/>
16. Keck PE. The use of divalproex. *J Clin Psychiatry Monograph*. 1997;15(4):18–19. Crisp AH. The sleepwalking/night terrors syndrome in adults. *Postgrad Med J*. 1996; 72(852):599–604. <https://pmj.bmj.com/content/postgradmedj/72/852/599.full.pdf>.
17. Wood JM, Bootzin RR. The prevalence of nightmares and their independence from anxiety. *J Abnorm Psychol*. 1990;99:64–8.
18. Boyden SD, Pott M, Starks PT. An evolutionary perspective on night terrors. *Evol Med Public Health*. 2018(1):100–105. doi:10.1093/emph/eoy010
19. Hwang SR, Hwang SW, Chu YC, Hwang JH. Association of sleep terror, walking or talking and tinnitus. *Journal of the Formosan Medical Association*. 2020 Apr 11. 120(1);145–149. doi:10.1016/j.jfma.2020.03.014
20. Chaudhury S, Kadiani A. Sleep assessment in psychiatry - To be awake to every possibility. *Med J DY Patil Vidyapeeth*. 2019;12(3):189–92. Doi:10.4103/mjdrdypu.mjdrdypu_214_18
21. Diaz-Abad M, Sanchez A, M, Kabir A, Konikkara J: A Case of Complex and Abnormal Behaviors at Night: The Role of the Epilepsy Monitoring Unit in Diagnosis. *Case Rep Neurol*. 2020;12(1):18–23. doi: 10.1159/000505230,
22. Shang-Rung Hwang, Sheng-Wei Hwang, Yia-Chi Chu, Juen-Haur Hwang, Association of sleep terror, walking or talking and tinnitus, *Journal of the Formosan Medical Association*. 2021; 1(1): 145–149. doi: 10.1016/j.jfma.2020.03.014.