

## Research Article

# ANTICONVULSANT PROFILE OF MENTAT AN EXPERIMENTAL STUDY WITH CLINICAL CO-RELATIONS

**Kumar A Amitabh\*, Reddy Kiran KP, Sagar P, Padmaja B**

**Department of Pharmacology, Narayana Medical College, Chinthareddypalem, Nellore, Andhra Pradesh, 524002. India.**

### ABSTRACT

Mentat, a polyherbal psychotropic preparation, is mostly used for its memory enhancing property. Only limited studies established that mentat possesses anticonvulsant property. The present study was carried out to evaluate anticonvulsant profile of mentat in animal models of convulsions, maximal electroshock seizures (MES) and pentylenetetrazole (PTZ) and to co-related with the clinical literature. Anticonvulsant activity of mentat was assessed in four groups of rats (n=6). The animals were treated orally (p.o.) with 300 and 600 mg/kg of mentat for seven days. On seventh day animals were subjected to MES and PTZ induced convulsions, phenytoin (25 mg/kg), intraperitoneally (i.p.) and sodium valproate (200 mg/kg, i.p.) were used as standards respectively. Mentat exhibits dose dependent anticonvulsant activity in MES and PTZ induced models of convulsions. Mentat in the dose of 300 mg/kg depicted significant anticonvulsant activity as compared to control in both the models, while at the dose of 600 mg/kg showed anticonvulsant activity, which was significant as compared to control and reference drugs in MES and PTZ induced models of convulsions. The results of this study if substantiated by further experimental research suggests that mentat has a broad spectrum antiepileptic activity. Although clinical trials have shown antiepileptic profile of mentat but these trials had few limitations such as small sample size and single institutional setting. This heralds the need to conduct controlled, blinded, multicentric clinical trial to evaluate the role of mentat in therapeutics of epilepsy.

**Keywords:** Antiepileptic, Mentat, Pentylenetetrazole, Seizures

### INTRODUCTION

Epilepsy is one of the most common neurological disorder characterized by seizures. Epileptic seizures result from excessive, abnormal, or hyper synchronous neuronal activity in the brain. It is clearly a major public health concern encountered in 5-10 persons per 1000. Onset of new cases occur most frequently in infants and the elderly. Epilepsy is generally controlled, although not cured, with drugs. However, over 30% of people with epilepsy do not have seizure control even with the best available medications.<sup>[1]</sup>

Moreover, most of the existing antiepileptic agents produce many undesirable side-effects including mental dullness, drowsiness, ataxia, hematologic changes, nausea, hirsutism, hypertrophy of gums, weight gain and congenital malformations.<sup>[2]</sup>

In recent times, focus on plant research has increased all over the world and a large body of evidence has been collected to show immense potential of medicinal plants used in various traditional systems as these products have less adverse effects. More than 13,000 plants have been studied

in last 5 years. The World Health Organization (WHO) estimates that 80% of the world population presently use herbal medicine for some aspect of primary health care needs. These medications may be taken in isolation or with allopathic medications.<sup>[3]</sup> In developing countries their use may be related to the unavailability of modern health care facilities. Major pharmaceutical companies are currently conducting extensive research on plant materials gathered from the rain forests and other places for their potential medicinal value.<sup>[4]</sup>

Mentat is a polyherbal psychotropic preparation which contains various ingredients reported in the ancient system of Ayurvedic medicine useful in the management of nervous disorders. It contains ingredients such as *Madhukaparni* (Indian Pennywort), *Ashvagandha* (*Withania somnifera*), *Vacha* (*Acorus calamus*), *Shatavari* (*Asparagus racemosus*), *Brahmi* (*Hydrocotyl asiatica*), *Amla* (*Emblica officinalis*), *Waterhyssop* (*Bacopa monnieri*), *Spikenard* (*Nardostachys jatamansi*) and *Shankhapushpi* (*Evolvulus alsinoide*).<sup>[5,10]</sup>

Many studies indicate that mentat is a safe polyherbal preparation with central action, it improves the mental quotient, memory span and stress threshold. The sedative and tranquilizing effects of mentat offer protection against convulsions and are beneficial in insomnia.<sup>[5]</sup> Most of the experimental studies show efficacy of mentat in models of chemoconvulsions (PTZ)<sup>[6]</sup>, efficacy of mentat in MES induced convulsions is not apparent. Therefore, the present study was carried out to evaluate the anticonvulsant profile of mentat in the models of electroconvulsions (MES) and chemoconvulsions (PTZ) and to co-relate with the available clinical literature.

## MATERIALS AND METHODS

### Animals

Adult Wistar albino rats weighing between 200-250 gm were used for this study. Rats were procured from central animal house of Narayana Medical College, Nellore. The animals were housed in cages in temperature-regulated rooms with air cooling and 12 h light and dark cycle, and had an access to food and water and libitum. They were allowed to acclimatize to the laboratory conditions for a period of one week. The study was approved by the Institutional Animal Ethics Committee (proposal number 7/2010/NMC), Narayana Medical College and all the experiments were performed as per the Committee for the purpose of control and supervision on experiments on animals (CPCSEA) guidelines.

### Drugs & Chemicals

Mentat (The Himalaya Drug Co.), sodium valproate (Sun Pharma), phenytoin (Pfizer), Pentylenetetrazole (Sigma Aldrich Bengaluru).

### Assessment of Anti-convulsant Activity

#### Grouping

Each model consists of four groups, each group containing 6 animals which were allocated randomly (Tables 1 and 2). Phenytoin and Sodium Valproate were used as reference drug to check anti-convulsant activity in MES and PTZ induced convulsions respectively.

Groups are divided as follows,

Group I Control group, normal saline 10 ml/kg

Group II Standard drugs Phenytoin (25 mg/kg) and Sodium Valproate (200 mg/kg)

Group III Mentat 300 mg/kg

Group IV Mentat 600 mg/kg

Control animals (Group I) received equal volume of normal saline 10 ml/kg intraperitoneally (i.p.). Standard drugs like phenytoin and sodium valproate were administered to Group II (standard group) (i.p.) for MES and PTZ induced convulsions respectively. Mentat 300 mg/kg and 600 mg/kg were given orally (p.o.) twice a day for seven days to Group III and IV rats respectively. On the seventh day animals were subjected to MES and PTZ induced seizures.

#### **Maximal electroshock seizures (MES) <sup>[7]</sup>**

In this method, electrical stimulation was applied via clipped ear electrodes (moistened with saline solution before each application) which delivered a constant current of 150 mA current for 0.2 seconds. Decrease in the duration of tonic hind limb extension was taken as an index of anticonvulsant activity. Parameters observed were time for onset and duration of tonic hind limb extension (THE) in seconds.

#### **Pentylentetrazole (PTZ) induced seizures <sup>[7]</sup>**

The unstrained rats were injected with pentylentetrazole (70 mg/kg body wt i.p.) one hour after test drug (mentat 300 and 600 mg/kg p.o) and standard drug (sodium valproate i.p.) and occurrence of the first generalized clonus (repeated clonic seizures of the fore and hind limbs lasting over 5 minutes with an accompanying loss of righting reflex) or jerky movements were recorded during individual observation for one hour. The onset and duration of both were observed. Delay in the onset of clonic convulsions was taken as an index of anticonvulsant activity.

#### **Statistical Analysis**

The data was collected in case record forms and entered into excel spreadsheet 2007. Statistical analysis was performed using Microsoft Excel-2007 and Sigma Graph pad prism version-5 USA. Data was described as Mean (Standard deviation).<sup>[8]</sup> One way ANOVA followed by Dunnett's test to compare control with all other columns and Newman-Keuls multiple comparison test was used for analysis of data between the inter individual groups. For all inferential statistical tests a two tailed  $P < 0.05$  was considered significant. All the results of test drug [mentat 300 and 600 mg/kg] were compared with control as well as standard groups.

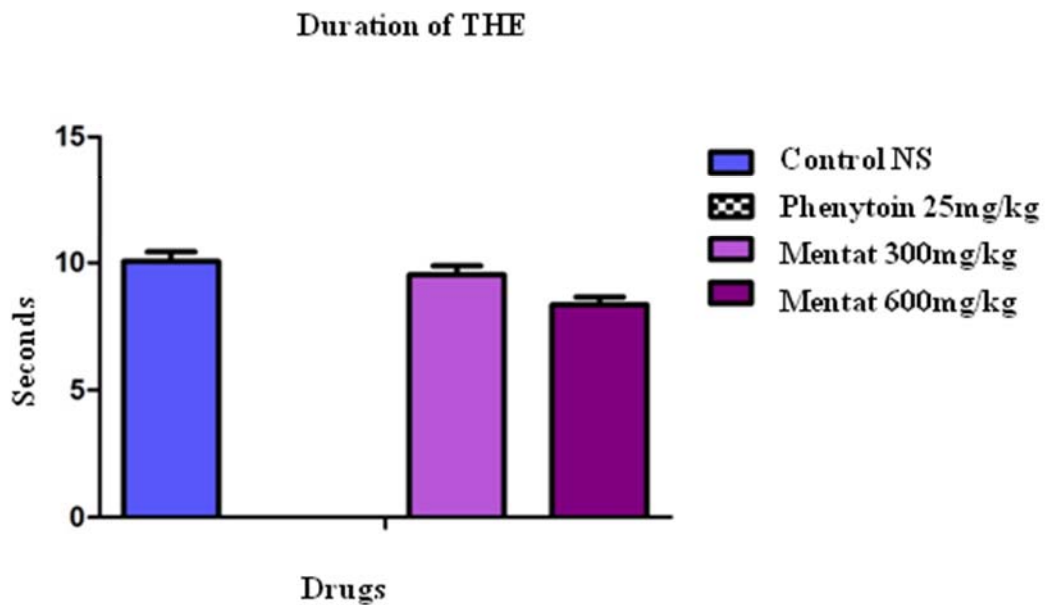
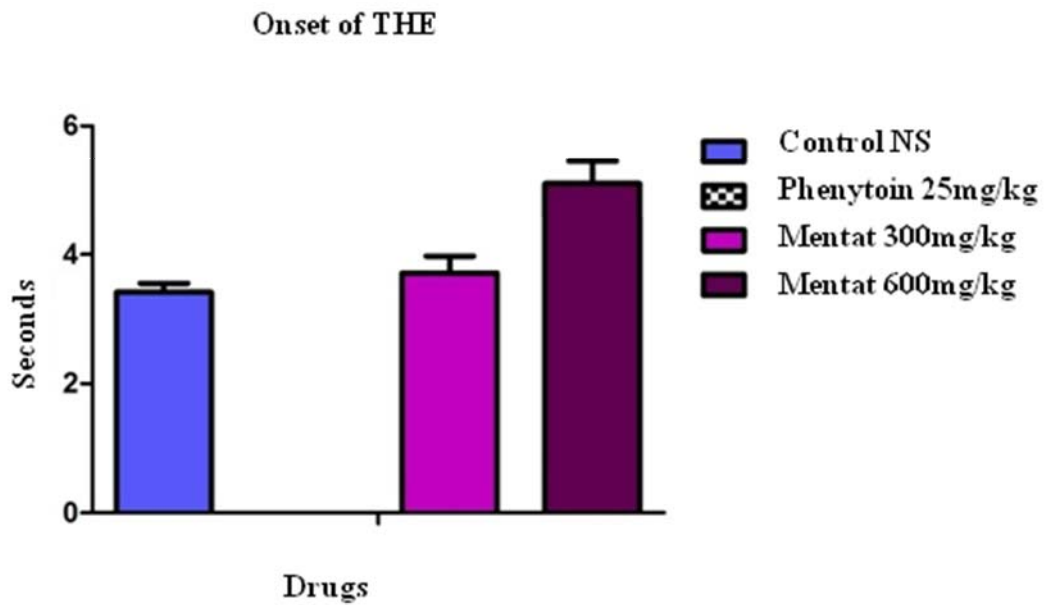
Phenytoin (Group II) completely abolished THE. Mentat 300 mg/kg (Group III) significantly delays the onset ( $p < 0.05$ ) and duration ( $p < 0.01$ ) of THE as compared to control (Group I) only. Whereas mentat 600 mg/kg (Group IV) significantly delays the onset ( $p < 0.001$ ) and duration ( $p < 0.001$ ) of THE as compared to the control (Group I) and the standard (Group II).

The onset of clonic convulsions in Group II (sodium valproate) was 10.82(1.07) minutes. Mentat 300 mg/kg (Group III) significantly delays the onset of clonic convulsions ( $p < 0.05$ ) as compared to the control (Group I) only. Whereas mentat 600 mg/kg (Group IV) significantly delays the onset of clonic convulsions ( $p < 0.001$ ) as compared to the control (Group I) and the standard (Group II).



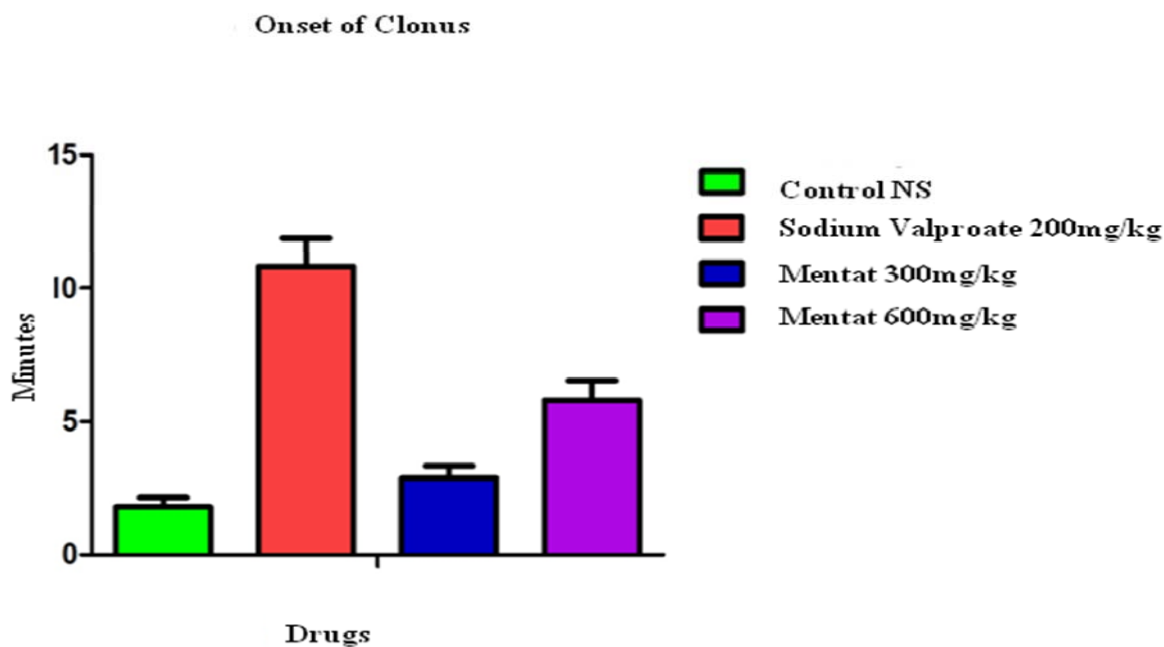
Graph A: Effect of mentat on maximal electro shock [MES] induced convulsions in rats.

(as per Table 1)



**Table 2: Effect of mentat on PTZ induced convulsions in rats (n=6)**

S.NO	Group & Dose (mg/kg)	Onset of clonic convulsions in minutes mean ( SD)
1.	Group I : Control (NS)	1.79(0.34)
2.	Group II : Sodium Valproate 200 mg/kg (i.p)	10.82(1.07)** <sup>a</sup>
3.	Group III : Mentat 300 mg/kg(p.o)	2.89(0.45)* <sup>a</sup>
4.	Group IV : Mentat 600 mg/kg(p.o)	5.81(0.72)** <sup>a,b</sup>
** p<0.001                      * p<0.05		
a- when compared with control.    b- compared with standard		

**Graph B: Effect of mentat on PTZ induced convulsions in rats (as per Table 2)**

## DISCUSSION

The present study was aimed at evaluating the antiepileptic property of mentat in comparison with standard drugs using animal models. Mentat is a polyherbal psychotropic preparation which contains many indigenous ingredients of ayurvedic medicine. The actions of mentat is nothing but the synergistic activity of the polyherbal compounds present in mentat. It is mainly used for its memory enhancing property.<sup>[5]</sup>

In the present study mentat was used in doses of 300 and 600 mg/kg. Mentat showed a dose dependent anticonvulsant effect in both, MES and PTZ models of convulsions. At higher dose (600 mg/kg) mentat showed a significant antiepileptic activity as compared to control (Group I) and standard drug (Group II) in both the models of convulsions.

Though there are no direct studies available which correlates with our findings showing dose dependent anticonvulsant effect of mentat on MES model, the probable mechanism could be due to synergistic action of *Bacopa monnieri* and *Nardostachys jatamansi*.

Kaushik et al (2009) showed that *Bacopa monnieri* decreased THE by nearly half the extension time in control.<sup>[9]</sup> Babu et al (2010) showed that the ethanol extract of *Nardostachys jatamansi* considerably increased the seizure threshold in the experimental model of generalized tonic-clonic seizures and combination of phenytoin with *Nardostachys jatamansi* shows synergistic action on MES. Since both these are present in mentat, thus mentat can also decrease the duration of THE in MES model.<sup>[10]</sup> The MES model has served to identify antiepileptic drugs that are generally effective in generalized tonic clonic seizures. Shukia et al concluded the

efficacy of *Bacopa monnieri* in models of convulsions is due to its GABA-ergic activity.<sup>[11]</sup>

We assessed the anti-epileptic activity of mentat using PTZ induced convulsions model, as this test is used for screening of drugs effective in petit mal epilepsy or absence seizures. Present study showed that mentat 300 mg/kg (Group III) significantly delays the onset of clonic convulsions ( $p < 0.05$ ) as compared to the control (Group I) only. Whereas mentat 600 mg/kg (Group IV) significantly delays the onset of clonic convulsions ( $p < 0.001$ ) as compared to the control (Group I) and the standard (Group II).

Our study is supported by the findings of Kulkarni et al (1993). In their studies they showed that acute administration of mentat to ethanol withdrawn mice showed protection against PTZ induced convulsions. The animals showed only mild clonic convulsions followed by recovery. Chronic administration of mentat followed by ethanol for 6 days exhibited only mild clonic seizures with delayed onset, and 25% mortality following administration of PTZ on day 7 in mice, whereas 60% mortality in control. This reduction in mortality may be because of the interaction of mentat with GABA benzodiazepine receptor complex. Mentat modulates GABA-A receptor which may result in opening of chloride ion channels leading to hyperpolarization of neurons thereby inhibiting seizures.<sup>[12]</sup>

Kulkarni et al (1995), also showed that pretreatment with mentat offered a significant protection both during the development of PTZ induced kindling and also once kindling was established. It may be due to potentiation of GABA-A neurotransmission on acute as well as chronic treatment of mentat.<sup>[6]</sup>



Mentat contains Indian Pennywort (*Madhukaparni*) which possesses antiepileptic properties and is commonly used as an adjuvant to epileptic drugs. Mentat balances amino acid levels, which is useful in treating affective disorder and in preventing cognitive impairment. Mentat reduces an endogenous monoamine oxidase inhibitor, tribulin, which is elevated during anxiety. The calming effects of mentat are useful in treating insomnia and convulsions, mediated by enhanced GABA-ergic neurotransmission.<sup>[16]</sup>

Majumdar et al (2001), conducted a placebo-controlled clinical study with 50 children having history of febrile convulsions. They were divided into two groups with 25 children in each group. The study showed that children responded well to mentat syrup with regard to both the prevention of recurrence of febrile convulsions and improvement in the behavioural pattern. They observed that 9 out of 25 children on mentat syrup had febrile episodes during the study period but none of them suffered from febrile convulsions. On the other hand, all the children in the placebo group showed convulsions.<sup>[13]</sup>

Banerjee et al (1994), conducted a double-blind, placebo-controlled clinical trial with sixty patients belonging to the age group of 15-45 years, with idiopathic epilepsy. They showed that there was decrease in frequency and duration of each seizure in the mentat-treated group of resistant epilepsies and doses of antiepileptic were reduced. They concluded that there may be an interaction with the endogenous opioid system like enkephalin or  $\beta$ -endorphin which raises the seizure threshold and protect individuals from seizures.<sup>[14]</sup>

Moharana & Moharana (1994), conducted clinical trial with 31 adults belonging to the age group of 23- 42 years. Their observation reveals that mentat 2

tablets two times a day, along with other antiepileptic drugs for six weeks brought significant reduction in seizure frequency and no adverse drug reactions were reported, indicating that mentat is a helpful adjuvant to conventional antiepileptic drugs.<sup>[1]</sup>

Pharmacokinetic studies on mentat when used along with standard antiepileptic drugs showed that there is an increase in the bioavailability of carbamazepine and suppression of phenytoin metabolism when co-administered with mentat. Thus mentat can be used as an add-on to enhance the efficacy of these anti-epileptic drugs. This synergistic action could lead to reduction in the doses of phenytoin and carbamazepine thereby reducing their toxicity.<sup>[15]</sup>

### Conclusion

Traditional medicines have been used to alleviate the suffering of human beings since the dawn of human civilization. Despite their wide spread usage traditional medicines have not been evaluated scientifically with regard to their safety, efficacy and has many limitations. In our study, mentat shows dose dependent anti-epileptic activity and it is efficacious in both the experimental models of convulsions (MES & PTZ). However, clinical studies in humans as discussed above, have not been properly randomized, blinded, controlled or had poor sample size. This provides an impetus to carry out randomized, controlled, double blind, multicentric trials in future to evaluate the role of mentat in the therapeutics of epilepsy.

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