Dear Editor,

Barbiturate is a potent substance which forms a quintessential part of the NDPS Act. The substance is categorized under the psychoactive groups of drugs and is essentially a drug that possesses both hypnotic and sedative properties. The precursor for barbiturate is barbituric acid which is a condensation product of malonic acid and urea. However, barbituric acid itself is not a centrally acting depressant. Diethylbarbituric acid (Veronal) is the first ever barbiturate with hypnotic properties that was used as early as 1903 (Hadjihambi et al., 2020). The drug induced sleep both in human and animals. The substance was also called as barbital. Later in the year 1912, a second barbiturate drug, phenobarbitone was introduced into clinical practice which had both sedative and hypnotic properties. The phenomenal success of both these drugs announced the beginning of the barbiturate era. Their influence as the pre-eminent sedative-hypnotic agents was felt for over half a century. Although several so-called non-barbiturate drugs attempted to displace the barbiturates from their pinnacle from time to time, it was not until 1961 when a substance named chlordiazepoxide was introduced into the market that their position was seriously challenged (Velle et al., 2021). Several earlier studies have reported the characteristic features and the severity of the barbiturate withdrawal syndrome. In cases of mild withdrawal syndrome, symptoms like apprehension, hyperexcitability, mild tremors, loss of appetite and piloerection were observed. An intermediate withdrawal syndrome exhibited tightness in the muscles, extreme tremors, sudden loss of body weight, altered motor activity, ex-
cessive nausea, and vomiting (Sharpe et al., 2020). The hallmarks of a severe withdrawal syndrome are convulsions, delirium or hallucination and hyperthermia or unusually high fever. The severity of withdrawal syndrome has been shown to depend on the frequency of drug administration and the duration of action of the drug. We review recent research on the role of barbiturates in brain disorders in this letter (Table 1).

**Table 1: Recent study on the role of barbiturates in brain disorders**

| Brain disorder         | Key findings                                                                                                                                                                                                 | Reference                  |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Epilepsy               | **Brandt et al.** reported several key advantages of bumetamine over bumetanide in targeting the nervous system. Some of these are; the potential of bumetamine to regulate diuresis, ability to render the drug more permeable and causing increased efficacy of the drug which in turn enhances the antiepileptic potential of phenobarbital. | **Brandt et al., 2018**    |
|                        | **Klein et al.** showed that both carbamazepine and phenytoin produced a far lesser therapeutic effect against focal nonconvulsive seizures, whereas valproate and levetiracetam revealed a moderate activity and phenobarbital and diazepam demonstrated marked anti-seizure effects. In addition, all AEDs are shown to restrain generalized convulsive seizures. | **Klein et al., 2015**     |
|                        | The antiepileptic activity of phenobarbital was enhanced when compared with bumetanide. Observations in the rat kindling model, namely BUMS (N,N-dimethylaminoethylester) were reported to justify this finding. | **Töllner et al., 2014**   |
|                        | The findings from this study have shown that N-methylation completely diminishes the Pgp affinity of barbiturates.                                                                                                                                                 | **Mairinger et al., 2012** |
|                        | The results obtained from the investigations suggested that, phenobarbital potentiates the activity of glutaprine and sodium valproate, thereby significantly minimizing their doses, and reducing the risk of side effects when these drugs are administered in higher doses and for a longer duration. | **Murphy et al., 2020**    |
| Neonatal seizure       | **The children who were not administered daily with phenobarbital had reported a higher incidence of epileptic episodes. However, these were primarily observed to be febrile seizures. The occurrence of pre-seizures and other abnormalities were also seen to be relatively high.** | **Sakuma et al., 2020**    |
|                        | Findings from this study have shown that the predisposing factors in infant subjects were oxygen deprivation, nerve related problems, and earlier barbiturate administration. Interestingly, in premature neonate extreme apnea was reported to be a predisposing factor. | **Specchio and Pietrafusa, 2020** |
|                        | **The results from this study had pointed out that prenatal PHB affected the anatomical maturation of the hippocampal architecture. Therefore, administration of PHB in management of such conditions is questionable.** | **Schizodimos et al., 2020** |
|                        | Thyroidal secretions were observed to be decreased in neonates administered with phenobarbitone. In addition, neural deficiencies and structural irregularities in neuronal tissues were seen in phenobarbitone use. Neuronal studies further revealed decreased sensitivity of DBA in subjects who were administered with phenobarbitone. The authors also elaborated on the existence of interactions between several genotypes as the nervous system developed. | **Hadjihambi et al., 2020** |
|                        | Administration of barbiturate drugs in infants for seizure preventive measures is not often recommended for normal clinical procedures, as incidences of death were reported in several cases. | **Young et al., 2016**     |
Brain tumor studies. Lack of suitable supporting studies have made it further challenging.

Two separate groups were studied. The findings suggest no drastic changes or differences among the study cohorts, in terms of adverse events. In addition, there were no fatalities due to BCT. The conclusions suggested efficient monitoring of refractory intracranial hypertension (RICH) after surgery.

From the findings of the study, it was evident that the strategy was focused to improve extreme deficiency of potassium in the blood. The findings also were strategized to prevent paroxysmal, fatal, rebounding potassium levels in the blood. Inspite of such efforts, the subjects who received the Barbiturate coma therapy (BCT) still reported and presented with having low grade hyperkalaemia.

Two major groups, namely the intervention group and the control group were studied. The findings suggested no significant differences in controlling epileptic episodes in the brain tumor subjects. Subjects who were on antiepileptic medications carried a higher risk of developing complications. These findings however may not be applied for drugs other than phenytoin, phenobarbital, and divalproex sodium.

Administration of phenobarbital may result in grave anatomical alterations in the architecture of the microtubules. Phenobarbital is also known to cause the destabilization of c-Jun, Akt and ERK proteins during the signaling process. To conclude, the observations reveal that the migratory and proliferation mechanisms of pentobarbital are arrested due to the disturbances in the microtubule function. The suggested mechanisms involve the ERK, c-Jun MAPK and PI3K/Akt pathways.

The study reports that subjects with brain tumors may not benefit from seizure preventive medications if they did not have a past-history of convulsions.

Status epilepticus

The study reports that, compared to barbiturates, propofol can control RSE and shorten ATIPT in a more competent and appropriate manner. Moreover, the study also suggests that the drug does not increase the occurrence of hypotension and CFR.

The study reported that the recurrence rate for late seizures was 13.6 % after having a strong influence with antiseizure drugs (ASD) in subjects having new onset status epilepticus (NOSE). The study also highlights that the probability of the convulsions to reoccur may be high in subjects with refractory status epilepticus (RSE) who were on barbiturate therapy. Further detailed and in depth studies are required to arrive at a proper conclusion.

The study reports that VPA (valproate) and PB (phenobarbital) were more effective than PHT (phenytoin/fosphenytoin) in subjects with SE (status epilepticus). However, PHT is not proven to be effective and is also expensive, which is a drawback when compared to its rivals.

The authors show that moderate-dose parenteral PB (phenobarbital) was efficient in attaining considerable seizure management in non-comatose refractory SE patients. None of the patients required ventilatory support. The authors conclude that PB dosages beneath those in recent guidelines may be sufficient to stop SE without clinically significant cardiopulmonary complications.
The study reported that PB (phenobarbital) at a dose greater than 100 µg/ml was found to be beneficial in adult subjects with refractory status epileptic (RSE). Furthermore, therapeutic plasma exchange has no effect on the amount of PB found in plasma.

**Intracranial pressure**

The findings from this study indicate that barbiturates, when used in a modern NICU (neurointensive care unit), serves as a promising strategy to safely reduce intracranial pressure without causing any extreme adverse effects in younger population who suffer from refractory intracranial hypertension (RICH) with potential long-term benefits.

The observations from this study discuss about the significance of hypothermia which was caused by pentobarbital. The findings suggest that a combination of barbiturates with other suitable prescribed medication would be beneficial in post-operative refractory intracranial hypertension. This may also be effective in overcoming the effects of intraoperative cranial inflammation in younger patients with brain injury.

The study reports that, unlike short-acting barbiturates, drugs like phenobarbital which have sustained pharmacological action may not be an appropriate choice of drugs when it comes to surgical induction. Phenobarbital may be helpful to decrease the metabolism in the brain and thereby decrease the intracranial pressure. However, phenobarbital causes several unwanted actions, the principal one being hypotension. This may tilt the balance negatively wiping off the beneficial effects.

According to Shein et al. intracranial pressure was observed to be lowered after phenobarbital administration. However, hypertonic saline was seen to have more merit as the first-line drug for treating intracranial hypertension, as it regulated the sympathetic cerebral hemodynamics and produced the fastest resolution of intracranial hypertension.

In this study, the authors showed that intracranial pressure fell after administration of HTS (hypertonic saline), mannitol, or barbiturates, which showed continued improvement after 2 hours.

**Conflict of interest**

The authors declare no conflict of interest.

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