

# PHENOBARBITONE: INDIAN CONSENSUS DOCUMENT



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# Phenobarbitone: Indian Consensus Document



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# Core Committee and Contributors

## **Man Mohan Mehndiratta - Convener**

Director;  
Professor & Head,  
Department of Neurology,  
Janakpuri Super Speciality Hospital,  
New Delhi

## **P. Satishchandra**

Director/Vice Chancellor and Senior Professor of Neurology,  
National Institute of Mental Health & Neuro Sciences (NIMHANS),  
Bengaluru, Karnataka

## **Satish Jain**

Director, Indian Epilepsy Centre  
New Delhi

## **Sangeeta Ravat**

Head, Department of Neurology  
Seth G.S. Medical College and King Edward Memorial Hospital  
Mumbai, Maharashtra

## **Parampreet S. Kharbanda**

Additional Professor Neurology & In-charge Comprehensive  
Epilepsy Program,  
Department of Neurology,  
Postgraduate Institute of Medical Education & Research (PGIMER),  
Chandigarh

## **Sita Jayalakshmi**

Senior Consultant Neurologist,  
Krishna Institute of Medical Sciences,  
Secunderabad, Telangana

## **Manjari Tripathi**

Professor, Department of Neurology  
Neurosciences Centre,  
All India Institute of Medical Sciences  
New Delhi

**Sheffali Gulati**

Professor of Pediatrics,  
Chief of Child Neurology Division, Department of Pediatrics  
All India Institute of Medical Sciences,  
New Delhi

**Suvasini Sharma**

Assistant Professor,  
Department of Pediatrics,  
Lady Hardinge Medical College and Associated Kalawati Saran  
Children's Hospital,  
New Delhi

**Pravina Shah**

Consultant Neurologist  
Fortis Hospital, Mulund, Mumbai, Maharashtra  
Ex. Head of Neurology  
Seth G.S. Medical College and King Edward Memorial Hospital,  
Mumbai, Maharashtra

**K.P. Vinayan**

Professor and Head  
Division of Pediatric Neurology,  
Department of Neurology,  
Amrita Institute of Medical Sciences  
Kochi, Kerala

**Sanjeev Thomas**

Professor of Neurology and  
Head of R. Madhavan Nayar Centre for  
Comprehensive Epilepsy Care  
Department of Neurology,  
Sree Chitra Tirunal Institute for Medical Sciences and Technology  
Thiruvananthapuram, Kerala

**Atma Ram Bansal**

Neurologist and Epileptologist  
Medanta—The Medicity  
Gurgaon, Haryana

**Atam Preet Singh**

Consultant Epileptologist and Head—Epilepsy  
Department of Neurology,  
Fortis Hospital, Noida, Uttar Pradesh

## **ELSEVIER INDIA**

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### **EDITORIAL OFFICE**

Elsevier, a division of Reed Elsevier India Private Limited  
14th Floor, Building No. 10B, DLF Cyber City, Phase-II,  
Gurgaon, Haryana – 122002, India.  
Telephone: + 91-124-4774444  
Fax: + 91-124-4774100



# Phenobarbitone: Indian Consensus Document

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## STATEMENT OF NEED

Neurology, as a branch of medicine, is a superspecialty that requires knowledge of a wide range of clinical presentations. Because of the diversity of clinical conditions encountered and the modification of the presentation of these at various stages of growth and development, it takes longer to acquire the pattern recognition and to be able to recognize presentations of the common and rare conditions. Epilepsy is a common neurological disorder with 65 million people with epilepsy (PWE) worldwide and approximately more than 12 million in India. Two-third of PWE live in resource-limited countries.

In this age, where at times there seems to be an overabundance of information, it is important for the practicing clinician to have an authoritative source of quality advice and genuine practice wisdom. Keeping in mind the requirements of the society, the practitioners need to update themselves on the current approaches and the wide variety of choices now available. India has a distinct need for comprehensive programs about the drugs and disease conditions that fit into the Indian context of the situation. It has to be a continuous process that aims at updating the clinicians on the current scenario and clear the apprehensions based on scientific evidence and approaches the problem on the basis of the experience of the specialists in India who are among the stalwarts in this field.

This document provides a useful basis from which to view new and existing perspectives in usage and position of phenobarbitone in the management of epilepsy, coupled with the more traditional protocols. It will be a valuable update tool and reference point for the many professionals engaged in the field of Neurology.



# Have We Forgotten to Remember Phenobarbitone?

**Satish Jain**

In 1864, Johann Friedrich Wilhelm Adolf von Baeyer, of Bayer Pharmaceuticals fame, concocted a new compound 'malonylurea' and renamed this new compound 'barbituric acid'. Emil Fischer and Joseph von Mering uncovered the medical value of the barbiturates in 1903. In 1912, Bayer Pharmaceuticals introduced phenobarbital to the market under the name Luminal—an effective sleeping aid that exhibited properties as an anticonvulsant. Phenobarbital still remains an active component in the treatment of seizures, making it the oldest epilepsy medicine still in use.

Phenobarbital acts via enhancing the activity of  $\gamma$ -aminobutyric acid-A (GABA<sub>A</sub>) receptors, depresses glutamate excitability, affects sodium, potassium, and calcium conductance. Phenobarbital has always been considered a highly effective and inexpensive anti-epileptic drug (AED), effective in partial or generalized seizures (including absences and myoclonus), status epilepticus, Lennox-Gastaut syndrome, childhood epilepsy syndromes, febrile convulsions, and neonatal seizures. Common side effects include sedation, ataxia, dizziness, insomnia, hyperkinesia (children), mood changes (depression), aggressiveness, cognitive dysfunction, impotence, reduced libido, folate deficiency, rash, vitamin D deficiency, etc. It has a number of interactions with AEDs and other drugs and is now not commonly used as a first-line AED.

A meta-analysis of 4 major trials found no difference between phenobarbitone and phenytoin (PHT) in various primary outcome measures.<sup>1</sup> Some randomized trials performed in industrialized countries have reported higher discontinuation rates with phenobarbitone. Observational studies in rural and urban Tanzania, India, Nigeria, and Mali have confirmed the effectiveness of phenobarbitone in spite of long history of untreated seizures among patients. Phenobarbital still remains a popular choice even in some of the developed countries despite the reported adverse effects and its

being not used as a first-line AED. The Italian First Seizure Trial Group (FIRST) study showed that more physicians chose phenobarbitone as compared to carbamazepine, valproic acid, and PHT to initiate AED therapy after the first or second seizure.<sup>2</sup> Phenobarbital continues to occupy a unique position and is still the most widely prescribed AED in the world. Phenobarbital is recommended by the World Health Organization (WHO) as a first-line AED for partial and generalized tonic-clonic seizures in developing countries.<sup>3</sup>

Phenobarbital can be taken to be an 'ideal' AED since it is effective in most seizure types and is a genuine 'broad spectrum AED'. It has the longest half-life among all AEDs, is available in multiple formulations, is inexpensive and affordable, and does have some side effects but beneficial effects outnumber side effects. No other AED matches it in its overall usefulness for the last 100 years! Phenobarbital is lot cheaper than believed. It is thus the 'ideal drug for national epilepsy control programs'.

The efficacy of phenobarbitone has been established and is not in question, but its general use as a first-line drug is limited by its perceived potential to cause sedation and mental slowness. It has, thus far, been a classic example of 'pharmaceutically orphan drug'. Phenobarbital thus has a definite role in epilepsy management both in the developing and developed world even in the 21st century. Based on the knowledge gained in regard to pharmacogenetics and pharmacogenomics, we can modify some of the existing AEDs to produce better, cheaper, and safer molecules. We should try and identify the reasons for the harmful effects of phenobarbitone especially among children and elderly. Phenobarbital molecule can then be made safer and more acceptable—it is still effective and inexpensive!

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# Phenobarbital: Mechanism of Action, Pharmacokinetics, and Side-effect Profile

Parampreet S. Kharbanda, Pravina Shah and Sahil Mehta

## INTRODUCTION

Phenobarbital is one of the oldest anticonvulsant drugs in the therapeutic armamentarium of epilepsy. Serendipity has played role in discovery of many drugs in the field of medicine. Phenobarbital is one of them whose anticonvulsant properties were discovered by Alfred Hauptmann in February 1912.<sup>1</sup> The World Health Organization has recommended it as a first-line drug for partial and generalized tonic-clonic seizures in developing countries.<sup>2</sup> Despite its cognitive and behavioral side effects, its low cost and high efficacy make it a commonly used anti-epileptic especially in developing nations and even in some developed countries. Parenteral phenobarbitone is used in the treatment of status epilepticus (SE).

## MECHANISMS OF ACTION

The various animal models of epilepsy have demonstrated suppression of seizure activity by phenobarbitone. These include electroshock-induced convulsions, subcutaneous pentylenetetrazole-induced clonic seizures, and electrically kindled seizures.<sup>3</sup> However, it worsens spike wave discharges in the animal models of absence seizures.

The anti-epileptic effects of phenobarbitone are through various mechanisms. Most importantly, it interacts with  $\gamma$ -aminobutyric acid A (GABA<sub>A</sub>) receptor and facilitates GABA-mediated inhibition via allosteric modulation of the receptor. It increases the mean channel open duration of the chloride channel without affecting channel conductance or opening frequency.<sup>4,5</sup> The increase in chloride influx leads to hyperpolarization of the postsynaptic neuronal cell membrane causing inhibition of the transmission of epileptic activity. In contrast, benzodiazepines after binding to the GABA receptor increase opening frequency without affecting the open or burst duration.

Phenobarbital is also known to limit high-frequency repetitive firing of action potentials at higher serum concentrations like those achieved in SE. The mechanism is related to interference with  $\text{Na}^+$  and  $\text{K}^+$  transmembrane transport and conductance. Presynaptically, it also decreases the  $\text{Ca}^{2+}$  influx which results in the decreased release of excitatory neurotransmitters such as glutamate and aspartate.<sup>6</sup>

## PHARMACOKINETICS

Phenobarbital corresponds chemically to 5-ethyl-5-phenylbarbituric acid with an empirical formula of  $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3$ . The chemical structure is shown in Figure 1. The presence of a phenyl group at the C-5 position confers more selective anti-epileptic activity. It has a molecular weight of 232.23 and is a weak acid with  $\text{pK}_a$  of 7.3.<sup>7</sup> It has limited water and lipid solubility in its free acidic form. Most formulations of phenobarbitone contain sodium salt because of good water solubility.

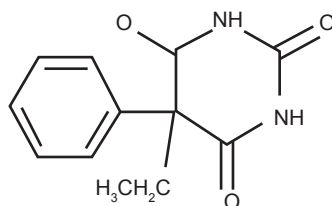


Figure 1. Chemical structure of phenobarbital.

It can be administered by both parenteral (intravenous and intramuscular) and oral routes. It is rapidly absorbed in the small intestine after oral ingestion and has a bioavailability of  $>95\%$ .<sup>8,9</sup> The volume of distribution ranges from 0.36 L/kg to 0.73 L/kg in adult and 0.39 L/kg to 2.25 L/kg in newborns with plasma protein binding of 55%.<sup>7,10</sup> Protein binding is further decreased in pregnancy and newborns.

It reaches peak plasma concentration after 0.5–4 h after oral dosing and 2–8 h after intramuscular administration. Concentrations of phenobarbitone in cerebrospinal fluid (CSF) correlate with unbound serum levels.<sup>8,9</sup> This drug shows very little fluctuation during inter dose intervals of up to 24 h, making estimation of serum levels relatively easier.

Phenobarbital readily crosses the placenta and plasma concentrations in neonates are similar to those in the mother. It is also secreted in

breast milk in which its concentrations are 40% of those in plasma.<sup>11</sup>

The distribution of phenobarbitone into body tissues after intravenous administration occurs in a biphasic manner. During the first phase, the drug distributes rapidly into highly vascular organs such as liver, kidney, and heart but not into the brain. With the exception of fat, it distributes uniformly throughout the body during the second phase. This pattern of slow entry into brain (12–60 min) and late exclusion from fatty tissue is due to low lipid solubility of the drug. However, in SE, the delivery of drug to brain is much faster due to focal acidosis and increased cerebral blood flow.<sup>7</sup>

Phenobarbital is extensively metabolized in the liver and leads to formation of two major but inactive metabolites, p-hydroxyphenobarbital by aromatic hydroxylation, which undergoes sequential metabolism to a glucuronic acid conjugate, and 9-D-glucopyranosylphenobarbital by glucosidation. The cytochrome P450 enzyme system mainly CYP2C9 plays a major role in hepatic metabolism with minor contribution from CYP2C19 and CYP2E1.<sup>7</sup> Genetic polymorphism of the CYP enzymes alters their expression and is an important determinant of individual susceptibility to drug toxicity.<sup>12</sup> Around 20% of Asians are poor CYP2C19 metabolizers compared with 5% of white population. In contrast, variants of CYP2C9 are more prevalent among whites (around 35%) compared with African-American and Asian populations (< 10%).<sup>13</sup>

Around 20–25% of administered dose of phenobarbitone is renally excreted unchanged in the urine.<sup>14</sup>

Phenobarbital exhibits linear pharmacokinetics. The half-life of the drug is long approximately 3–5 days in adults and 1.5 days in children so it is usually given as once-daily dose.<sup>7</sup>

Phenobarbital can be withdrawn safely in patients on other maintenance anticonvulsants without increasing risk of withdrawal seizures. This is attributed to the long half-life of phenobarbitone.<sup>15</sup> Various studies have also corroborated the fact that withdrawal of phenobarbitone is not associated with exacerbation of seizures.<sup>16</sup>

Therapeutic drug levels for phenobarbitone range from 10 mg/L to 40 mg/L (43–172  $\mu\text{mol/L}$ ).<sup>17</sup> The conversion factor from mg/L to  $\mu\text{mol/L}$  for phenobarbitone is 4.31. Higher plasma concentrations of phenobarbitone are required to produce complete control of simple or complex partial seizures than tonic-clonic seizures.

Multidrug transporters especially P-glycoprotein at cerebral capillary endothelium play an important role in transport of anticonvulsants across blood brain barrier.<sup>18</sup> Phenobarbital is one of the substrates of P-glycoprotein. Expression of P-glycoprotein is partly determined by genetic polymorphism of the encoding gene, multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1).<sup>19</sup> Over expression of such drug transporters plays a crucial role in the phenomenon of drug-resistant epilepsy.

### PHARMACOKINETICS IN SPECIAL GROUPS

The half-life of phenobarbitone varies with age. Premature and full-term neonates have the longest half-lives (59–400 h), while it is shortest in infants aged 6 weeks to 12 months. Total clearance ranges between 5.3 mL/kg/h and 14.1 mL/kg/h in children aged between 8 months and 4 years.<sup>20</sup>

The clearance of phenobarbitone is reduced in the elderly. It is 2.5 mL/kg/h for patients >40 years of age compared to 4.9 mL/kg/h in those 15–40 years of age.<sup>21</sup>

The half-life of phenobarbitone is prolonged in patients with liver cirrhosis ( $130 \pm 15$  h).<sup>22</sup>

Pharmacokinetics of phenobarbitone is illustrated in Table 1.

<b>Table 1. Pharmacokinetics of Phenobarbital</b>	
<b>Indication</b>	<b>Partial and generalized tonic–clonic seizures, neonatal seizures; status epilepticus, febrile seizures</b>
Not useful	Absence seizures
Mechanism of action	Enhance GABA inhibition
Bioavailability	>95%
Time to peak levels after single dose	0.5–4 h
Protein binding	45–60%
Elimination half-life	3–5 days (adults), 1.5 days (children)
Main routes of elimination	Hepatic metabolism; CYP 450 inducer 25% renally excreted unchanged
Maintenance dose	Children : 4–8 mg/kg/day Adults: 60–240 mg/day

Volume of distribution	0.42–0.73 L/kg
Daily doses	1–2
Target plasma concentration	10–40 g/mL
Clearance	Age > 40 years, total clearance: 2.5 mL/kg/h Age 15–40 years, total clearance: 4.9 mL/kg/h Age 8 months to 4 years, total clearance: 5.3–14.1 mL/kg/h

GABA:  $\gamma$ -aminobutyric acid; CYP 450: cytochrome P450.

## DRUG INTERACTIONS

Phenobarbital is an enzyme inducer. It undergoes auto induction; so it increases its own clearance necessitating upward dose adjustment when prescribed as monotherapy. There are no well-documented pharmacodynamic interactions between phenobarbitone and other drugs except for the potentiation of central nervous system (CNS)-depressant effects with benzodiazepines and other barbiturates. Various pharmacokinetic interactions are cited below and in Table 2.

### Effect of Phenobarbital on the Pharmacokinetics of Other Drugs

Phenobarbital because of its metabolism by cytochrome P450 is involved in many drug interactions. Phenobarbital acts as a potent enzyme inducer by altering transcription of orphan nuclear receptors including pregnane X receptor and constitutive androsterone receptors.<sup>23</sup> Environmental (tobacco and alcohol) and genetic factors can influence the response of phenobarbitone as evidenced by studies in mono and dizygotic twins.

It results in increased clearance and reduced concentration of many drugs which undergo hepatic metabolism including other anticonvulsants (phenytoin, carbamazepine, valproate, and lamotrigine), oral contraceptives, Warfarin, corticosteroids, analgesics (paracetamol and meperidine), theophylline, verapamil, and some endogenous hormones (vitamin D). The effect of phenobarbitone on phenytoin levels is complex; it may simultaneously induce and inhibit phenytoin metabolism leading to unpredictable effects in individual patient.<sup>23</sup>

There are certain circumstances when induction of drug metabolism by phenobarbitone causes an increased production of toxic metabolites leading to toxicity. For example, metabolism

of acetophenetidin by phenobarbitone leads to formation of methemoglobin by production of a toxic intermediary metabolite (2-hydroxyphenitidin) especially in patients with inherited metabolic disorders.<sup>24</sup> It may also contribute to hepatotoxicity in combination with valproic acid by forming toxic metabolites of valproic acid.<sup>25</sup>

### Effects of Other Drugs on Pharmacokinetics of Phenobarbital

Valproate inhibits the metabolism of phenobarbitone leading to reduced clearance and prolongs half-life of phenobarbitone.<sup>26</sup> This is the most predictable and clinically important interaction in this group. There are increased chances of sedation and weight gain in patients on combination therapy with these two drugs. This interaction occurs more frequently in pediatric patients than adults. Furthermore, chances of valproic acid-induced hyperammonemia are increased in patients co-medicated with phenobarbitone.

Other drugs such as felbamate, clobazam, dextropropoxyphene, chloramphenicol, and phenytoin may inhibit metabolism of phenobarbitone levels.

**Table 2. Few Examples of Drug Interactions Involving Phenobarbital**

Acetazolamide	Increase phenobarbital levels
Phenytoin	Increase phenobarbital levels by 50–70%
Valproic acid	30–50% increase in phenobarbital levels
Oxcarbazepine	Increase phenobarbital levels by 15% at doses > 1200 mg/day
Clobazam	Phenobarbital enhances metabolism of clobazam
Oral contraceptives	Failure of oral contraceptives
Warfarin	Phenobarbital induces metabolism of warfarin
Steroids, antimicrobials, antineoplastic drugs	Decrease levels of drugs by phenobarbital



## **SIDE-EFFECT PROFILE**

Sedation and hypnosis are the principal side effects of phenobarbitone. Central nervous system effects such as dizziness, nystagmus, and ataxia are also common. In elderly patients, it may cause excitement and confusion, while in children, it may result in paradoxical hyperactivity.

### **Acute Alcohol Intoxication<sup>27,28</sup>**

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The use of barbiturates is contraindicated in patients with acute alcohol intoxication exhibiting depressed vital signs. The central nervous system depressant effects of barbiturates may be additive with those of alcohol. Severe respiratory depression and death may occur. Therapy with barbiturates should be administered cautiously in patients who might be prone to acute alcohol intake.

### **Drug Dependence<sup>27-29</sup>**

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Tolerance as well as physical and psychological dependence can develop, particularly after prolonged use of excessive dosages.

Abrupt cessation and/or a reduction in dosage may precipitate withdrawal symptoms. In patients who have developed tolerance to a barbiturate, overdose can still produce respiratory depression and death, and cross-tolerance usually occurs with other agents in the class.

### **Porphyria<sup>27,28</sup>**

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The use of barbiturates is contraindicated in patients with a history of porphyria. Barbiturates may exacerbate acute intermittent porphyria or porphyria variegata by inducing the enzymes responsible for porphyrin synthesis.

### **Rash<sup>27,28</sup>**

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Skin eruptions may precede rare but potentially fatal barbiturate-induced reactions such as systemic lupus erythematosus and exfoliative dermatitis, the latter of which may be accompanied by hepatitis and jaundice.

Barbiturate therapy should be withdrawn promptly at the first sign of a dermatologic adverse effect. However, cutaneous reactions may proceed to an irreversible stage even after cessation of medication

due to the slow rate of metabolism and excretion of barbiturates.

Patients should be advised to promptly report signs that may indicate impending development of barbiturate-related cutaneous lesions, including high fever, severe headache, stomatitis, conjunctivitis, rhinitis, urethritis, and balanitis. Rashes may be more likely to occur with phenobarbitone and mephobarbital.

### **Renal Dysfunction**<sup>27,28,30,31</sup>

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The long-acting barbiturate, phenobarbitone, is partially eliminated by the kidney. The plasma clearance of phenobarbitone may be decreased and the half-life prolonged in patients with impaired renal function. Therapy with phenobarbitone should be administered cautiously and initiated at reduced dosages in patients with renal impairment. Since approximately 75% of a mephobarbital dose is metabolized to phenobarbitone, the same precaution should be observed with mephobarbital.

### **Suicidal Tendency**<sup>27,28,32,33</sup>

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Anti-epileptic drugs (AEDs) have been associated with an increased risk of suicidal thoughts or behavior in patients taking these drugs for any indication. The increased risk of suicidal thoughts or behavior was observed as early as 1 week after starting AEDs and persisted for the duration of treatment assessed.

Therapy with AEDs should be administered cautiously in patients with depression or other psychiatric disorders. The risk of suicidal thoughts and behavior should be carefully assessed against the risk of untreated illness, bearing in mind that epilepsy and many other conditions for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Patients, caregivers, and families should be alert to the emergence or worsening of signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts or behavior.

### **Liver Disease**<sup>34-36</sup>

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Barbiturates are extensively metabolized by the liver. The plasma clearance of barbiturates may be decreased and the half-lives prolonged in patients with impaired hepatic function. Therapy with barbiturates should be administered cautiously and initiated at reduced dosages in patients with liver disease. Barbiturates are

not recommended for use in patients with cirrhosis, hepatic failure, hepatic coma, or other severe hepatic impairment.

### **Respiratory Depression<sup>27,28</sup>**

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Barbiturates may produce severe respiratory depression, apnea, laryngospasm, bronchospasm, and cough, particularly during rapid intravenous administration.

Therapy with barbiturates should be administered cautiously in these patients. Appropriate monitoring and individualization of dosage are particularly important.

Barbiturates, especially injectable formulations, should generally be avoided in patients with sleep apnea, hypoxia, or severe pulmonary diseases in which dyspnea or obstruction is evident.

### **Cardiovascular<sup>27,28</sup>**

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The intravenous administration of barbiturates may produce severe cardiovascular reactions such as bradycardia, hypertension, or vasodilation with fall in blood pressure, particularly during rapid infusion. Parenteral therapy with barbiturates should be administered cautiously in patients with hypertension, hypotension, or cardiac disease. The intravenous administration of barbiturates should be reserved for emergency treatment of acute seizures or for anesthesia.

### **Prolonged Hypotension<sup>27,28</sup>**

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Barbiturates should not be administered by injection to patients in shock or coma or who have recently received another respiratory depressant. The hypnotic and hypotensive effects of these agents may be prolonged and intensified in such patients.

### **Adrenal Insufficiency<sup>27,28</sup>**

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Barbiturates, especially phenobarbitone, secobarbital, and butabarbital, may diminish the systemic effects of exogenous and endogenous corticosteroids via induction of hepatic microsomal enzymes, thereby accelerating the metabolism of corticosteroids. In addition, barbiturates may interfere with pituitary corticotropin production. Therapy with barbiturates should be administered cautiously in patients with adrenal insufficiency. Patients with borderline hypoadrenalism should be monitored closely, and patients receiving steroid supplementation may require an adjustment in

dosage when barbiturates are added to or withdrawn from their medication regimen.

### **Depression<sup>32</sup>**

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Barbiturates depress the central nervous system and may cause or exacerbate mental depression. Therapy with barbiturates should be administered cautiously in patients with a history of depression or suicidal tendencies. It may be prudent to refrain from dispensing large quantities of medication to these patients.

### **Hematologic Toxicity<sup>37</sup>**

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Hematologic toxicity, including agranulocytosis, thrombocytopenic purpura, and megaloblastic anemia, has been reported rarely during use of barbiturates. Therapy with barbiturates should be administered cautiously in patients with pre-existing blood dyscrasias or bone marrow suppression. Blood counts are recommended prior to and periodically during long-term therapy, and patients should be instructed to immediately report any signs or symptoms suggestive of blood dyscrasia such as fever, sore throat, local infection, easy bruising, petechiae, bleeding, pallor, dizziness, or jaundice. Barbiturate therapy should be discontinued if blood dyscrasias occur.

### **Osteomalacia<sup>28,38,39</sup>**

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Rickets and osteomalacia have rarely been reported following prolonged use of barbiturates, possibly due to increased metabolism of vitamin D as a result of enzyme induction by barbiturates. Long-term therapy with barbiturates should be administered cautiously in patients with vitamin D deficiency.

### **Paradoxical Reactions<sup>27,28</sup>**

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Paradoxical reactions characterized by excitability and restlessness may occur in pediatric patients with hyperactive aggressive disorders. Such patients should be monitored for signs of paradoxical stimulation during therapy with barbiturates.

### **Teratogenicity<sup>40</sup>**

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Phenobarbital is associated with congenital anomalies such as dysmorphic face, Fallot tetralogy in heart, hydronephrosis, inguinal hernia with umbilical hernia, and congenial dislocation of the hip when exposed during the first trimester of pregnancy.

**Salient Features Regarding Pharmacokinetics of Phenobarbital**

- ▣ Prolonged half-life and once-daily dosing can help improve compliance.
- ▣ Little fluctuation during inter dose intervals of up to 24 h makes it easier to check plasma levels.
- ▣ Higher plasma concentrations might be needed for partial than generalized tonic-clonic seizures.

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# Literature Review—Key Studies and Systematic Reviews Related to Phenobarbitone

**Manjari Tripathi**

Phenobarbitone is one of the few anti-epileptic agents which have been in use for several decades. There are several studies of its use in the community as well in controlled clinical trials. This chapter reviews its use across the same in some of the key studies performed to see the efficacy of phenobarbitone.

Wang et al performed a large study on the efficacy of phenobarbitone in the community. The study had enrolled 2455 persons with epilepsy. Seizure outcomes were assessed at 6, 12, and 24 months. Seizure freedom was seen in 41%, 34%, and 26% of patients, respectively. More than 75% reduction of seizures was seen in 14%, 22%, and 31%, respectively. More than 51–75% reduction was seen in 11%, 12%, and 14%, respectively. Of the 72% who completed a 24 month of follow-up, 75% had 50% or more reduction of seizures and 25% were controlled. Retention rate at 1 year was 0.84 and at 2 years was 0.76. One percent discontinued medication due to side effects. More patients had drowsiness at the start of medication as compared to at the end (27% vs 8% at 24 months).

Another community-based randomized controlled study done in rural south India by Dr Mani (Yelandur study) reported in 2001 that in 135 patients with epilepsy, terminal remission ranged from 58% to 66%, respectively, for those who were compliant and had < 30 generalized tonic-clonic seizures. Adverse events were noted in 4% of patients.

The Cochrane review on the role of phenobarbitone for partial onset seizures and partial seizures by Nolan SJ et al in 2013 reviewed 4 trials and concluded that based on the studies, it was not clear on the usefulness on seizure control that either phenytoin (PHT) or phenobarbitone scored over each other. However, PHT was more likely to be retained. As the trials were not masked, there could have been a prejudice toward phenobarbitone resulting in more withdrawals.



Mattson in 1985 compared carbamazepine (CBZ), phenobarbitone, PHT, and primidone (PRI) in partial and secondarily generalized tonic-clonic seizures. They performed a 10-center, double-blind trial to compare the efficacy and toxicity of these 4 anti-epileptic drugs in 622 adults. Patients were randomly assigned to treatment with CBZ, phenobarbitone, PHT, or PRI and were followed for 2 years or until the drug failed to control seizures or caused unacceptable side effects. Overall treatment success was highest with CBZ or PHT, intermediate with phenobarbitone, and lowest with PRI ( $p < 0.002$ ). Differences in failure rates of the drugs were explained primarily by the fact that PRI caused more intolerable acute toxic effects, such as nausea, vomiting, dizziness, and sedation. Decreased libido and impotence were more common in patients given PRI. Phenytoin caused more dysmorphic effects and hypersensitivity. Control of tonic-clonic seizures did not differ significantly from the various drugs. Carbamazepine provided complete control of partial seizures more often than PRI or phenobarbitone ( $p < 0.03$ ). In this study, CBZ and PHT were recommended as the first choice for the single-drug therapy of adults with partial or generalized tonic-clonic seizures or in both.

A comparison of phenobarbitone, PHT, carbamazepine, or sodium valproate (VPA) for newly diagnosed adult epilepsy done in a randomized comparative monotherapy trial was reported by Heller et al. Fifty-eight patients were in the phenobarbitone group and 63 in the PHT group, 44% had partial epilepsy. Twenty-seven percent were seizure free and 75% entered 1 year of remission by 3 years of follow-up. No significant differences between the 4 drugs were found for either measure of efficacy at 1, 2, or 3 years of follow-up. The overall incidence of unacceptable side effects, phenobarbitone (22%) was more likely to be withdrawn than PHT (3%), carbamazepine (11%), and sodium VPA (5%). The authors concluded that the choice of drug would hence depend on toxicity and costs.

In 1996, a randomized comparative monotherapy trial of phenobarbitone, PHT, carbamazepine, or sodium VPA for newly diagnosed childhood epilepsy was reported by de Silva et al. Only 10 children were in the phenobarbitone group. The overall outcome with all 4 drugs was good. Twenty percent of children remained free of seizures and 73% had achieved 1-year remission by 3 years of follow-up. We found no significant differences between the drugs for either measure of efficacy at 1, 2, or 3 years of follow-up. The overall frequency of unacceptable side effects necessitating withdrawal

of the randomized drug was 9%. This total included 6 of the first 10 children assigned phenobarbitone; no further children were allocated this drug. Of the other 3 drugs, PHT (9%) was more likely to be withdrawn than carbamazepine (4%) or sodium VPA (4%).

Another comparison of phenobarbitone ( $n = 51$ ), PHT ( $n = 52$ ) with sodium VPA which was a randomized, double-blind study was published in *Indian Pediatrics* in 1996. Hyperactivity was the major side effect of phenobarbitone, observed in 22% of children. The authors concluded that all 3 drugs were equally effective in controlling seizures. Side effects were minimal with VPA followed by phenobarbitone. Though side effects were more frequent with PHT, most of them disappeared on adjusting drug dosage. They suggested that the least expensive phenobarbitone may be preferred as the first drug of choice but only for pre-school children. Valproate was advised for school-going children.

Pal et al in *Lancet* 1998 published the results of a randomized controlled trial to assess acceptability of phenobarbitone for childhood epilepsy in rural India. Forty-seven children received phenobarbitone and 47 received PHT. The mean log-transformed scores on the behavior rating scales did not differ significantly between the phenobarbitone and PHT groups ( $p = 0.97$ ). The odds ratio (OR) for behavioral problems (Phenobarbitone vs PHT) was 0.51 (95% CI 0.16–1.59). There was no increase in parents reporting on side effects for phenobarbitone. The authors found no difference in efficacy between the study drugs (adjusted hazard ratio for time to the first seizure from randomization 0.97 [0.28–3.30]).

A prospective multicentric study looking at cognitive effects of phenobarbitone in India by Satischandra et al was done but this was not a blinded study and the primary aim was to look for cognitive side effects and not efficacy. In this 1-year study, no deleterious effects on cognition were noted and there was no deterioration also in daily activities and depression.

The effect of phenobarbitone on pregnancy has been looked at in the European and International Registry of Antiepileptic Drugs and Pregnancy (EURAP) registry and of the major congenital malformations, 217 women were on phenobarbitone (166 were taking <150 mg and 51 were taking >150 mg). Congenital malformations were seen in 4.2 and 13.7, respectively. The increase in odds was

2.5 and 8.2 when compared to <300 mg of lamotrigine and within phenobarbitone comparison was an OR of 3.2. The numbers that were seizure free were 71% and 69%, respectively. A comparison of various studies listing problems with the use of phenobarbitone is given in Table 1.

**Table 1. Comparison of Various Studies Listing Problems with the Use of Phenobarbitone**

Study (year)	Subjects	Comments
Mani et al (2001)	135 (phenobarbitone:55)	4% on phenobarbitone while 43% on PHT had adverse effects.
Wang et al (2006)	2455 (phenobarbitone) patients	Phenobarbitone was well tolerated, few had mild reported adverse events and only 32 patients (1%) discontinued medication because of side effects.
Satischandra et al (2014)	75 (63 completed) adult patients with newly diagnosed epilepsy-prospective multicentric study	No worsening of cognitive or psychosocial functioning; good seizure control improvement in attention, executive functions, learning, memory, and intelligence. Self-report of cognitive impairment consequent to the epilepsy and its treatment showed a decrease. No deterioration in daily activities and depression.
Meador et al (1995)	59 healthy adults received phenobarbitone, PHT, or VPA	Those on phenobarbitone were worse (not significant) than either PHT or VPA; PHT and VPA were comparable.
Tudur Smith et al (2003)	684 patients	phenobarbitone and CBZ did not differ for the outcomes of 'time to 12 month remission' and 'time to first seizure' phenobarbitone more likely to be withdrawn indicating less tolerance as compared with CBZ.
Feksi et al (1991)	302 (249 completed the study)	53% seizure-free low drop-out rate, low rate of withdrawal due to adverse effects and acceptable compliance.

Adapted with permission from: Satischandra P, Rao SL, Ravat S, et al. *Epilepsy Res* 2014;108:928–36.

PHT: phenytoin; VPA: valproate; CBZ: carbamazepine.

What comes from the studies comparing Indian and western data/literature differs in terms that lesser side effects were observed in Indian data than the western data.

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# Phenobarbitone in the Management of Status Epilepticus

Sudhindra Vooturi, Sita Jayalakshmi

## INTRODUCTION

Phenobarbital or phenobarbitone is one of the handful orthodox medicines with a pedigree longer than 100 years. It is the most widely used anti-epileptic drug (AED) in the developing world.<sup>1</sup> The bioavailability of phenobarbitone, a  $\gamma$ -aminobutyric acid (GABA)-mediated inhibitor, is over 95% with approximately 50% protein binding and half-life of 72–144 h. Lower cost of phenobarbitone than any other AED in current use<sup>2</sup> makes it affordable and suitable for use in low- and middle-income countries where cost effectiveness is a priority. In fact, the World Health Organization recommends phenobarbitone as first-line therapy for partial and generalized tonic-clonic seizures in developing countries.<sup>3</sup> The current review focuses on the role of phenobarbitone in the management of status epilepticus (SE), with emphasis on its tolerability and efficacy.

## PHENOBARBITONE IN STATUS EPILEPTICUS (TABLE 1)

A substantial number of physicians prescribe phenobarbitone as the initial line of treatment for generalized convulsive status epilepticus (GCSE).<sup>4</sup> Shaner et al have reported shorter cumulative convulsion time, response latency time, median cumulative convulsion time, and median response latency times in consecutive patients with GCSE treated with phenobarbitone than that of diazepam/phenytoin regimen. The frequencies of intubation, hypotension, and arrhythmias were similar in the two groups.<sup>5</sup> The loading dose of phenobarbitone in SE is 20–40 mg/kg and the maintenance dose is 4–8 mg/kg/day in children and is 60–240 mg/day in adults given at 1–2 daily doses with a target plasma concentration of 10–40  $\mu\text{g/mL}$ .<sup>6</sup>

Phenobarbitone is one of the second-line AED in the management of convulsive SE as per guidelines in the management of SE. Treiman

et al,<sup>7</sup> in the US Veterans Affairs Cooperative study, evaluated the treatment efficacy of initial management of GCSE by phenobarbitone, diazepam plus phenytoin, phenytoin, and lorazepam. The results of the study indicated that phenobarbitone was no less effective than lorazepam (the best AED) in control of overt GCSE. The same study also observed that phenobarbitone is similar to other AEDs in protecting against recurrence of GCSE over 12 h time period. Moreover, in the study population, the risk of AED-related adverse events was similar across all the four drug groups. Furthermore, in nearly half of the patients, phenobarbitone was successful as the first-line therapy.

<b>Table 1. Phenobarbitone in Status Epilepticus<sup>1</sup></b>	
<b>Indication</b>	Convulsive SE, nonconvulsive SE in children and adults, refractory SE
<b>Bioavailability</b>	Approximately 95%
<b>Standard dosage in SE</b>	20–40 mg/kg/day
<b>Maintenance dose:</b>	
<b>In children</b>	4–8 mg/kg/day
<b>In adults</b>	60–240 mg/day
<b>Route of elimination</b>	Metabolized in liver; one-fourth excreted unchanged in urine
<b>Advantages of phenobarbitone</b>	Estimated efficacy of 73.6%, Broad spectrum of action Affordability Comparative efficiency with other AEDs Neuroprotective effect
<b>Common adverse effects</b>	Respiratory depression, hypotension, severe sedation

SE: status epilepticus; AED: anti-epileptic drug.

In patients where the SE is resistant to first-line administration of benzodiazepines, phenobarbitone has been extensively used effectively as the next line of therapy, based on the findings reported in Veteran affairs study.<sup>7</sup> Moreover, in patients with established SE, lacosamide, levetiracetam, and valproate (VPA) have recently been introduced. Yasiry and Shorvon,<sup>8</sup> in a meta-analysis of literature available on treatment of benzodiazepine-resistant SE, have recently suggested that phenobarbitone has an estimated efficacy of 73.6% (95% CI: 58.3–84.8%). Significant advantage of phenobarbitone in

addition to this efficacy is its potential neuroprotective effect. The study further added that there is not enough evidence to support the routine use of lacosamide. Furthermore, despite suggestive lower adverse events of levetiracetam in pediatric, adult, and elderly populations, the experience is relatively limited. Importantly, the reported efficacy of levetiracetam (68.5%) in the study was lower than the efficacy of phenobarbitone. Brigo et al,<sup>9</sup> in a reference-based indirect comparison of intravenous VPA and intravenous phenobarbitone emphasized on the insufficiency of evidence to demonstrate the superiority of VPA over phenobarbitone in the management of convulsive SE.

### PHENOBARBITONE IN REFRACTORY STATUS EPILEPTICUS

Patients where SE persists despite first-line and second-line AEDs are suitably categorized as refractory SE (RSE) and it is associated with high morbidity and mortality. Tiamkao et al<sup>10</sup> reported that very high dose phenobarbitone is effective in the management of adult and elderly patients with RSE. Similarly, Lee, Liu, and Young<sup>11</sup> have shown that very high dose phenobarbitone is effective in seizure control with milder side effects than thiopental infusion in childhood RSE. Crawford et al reported 50 children with RSE treated with very high dose phenobarbitone (30–120 mg/kg) and phenobarbitone was successful in controlling SE in all patients.<sup>12</sup> Additionally, therapeutic concentrations and seizure control after enteral loading of phenobarbitone gave encouraging results with minimal side effects in South African patients with RSE.<sup>13</sup> However, children with prolonged convulsive SE with intravenous phenobarbitone had significantly higher rates of adverse events (74% vs 24%) than those treated with intravenous VPA.<sup>14</sup>

### ADVERSE EFFECTS WITH PHENOBARBITONE

Like most other AEDs, phenobarbitone is associated with dose-dependent adverse effects that limit its use. These adverse effects include respiratory depression, hypotension, severe sedation, tolerance, and the potential for drug interactions.<sup>15</sup> Most of the reported side effects of phenobarbitone were extrapolated from unlabeled randomized control studies done predominantly in epilepsy patients from developed countries. Zhang, Zeng, and Li in a systematic review of side effects of phenobarbitone suggested that phenobarbitone was associated with higher rate of adverse drug reaction withdrawal in comparison with carbamazepine, phenytoin,

and VPA.<sup>16</sup> Furthermore, the study did not find significant differences between the drugs for total withdrawal indicating that the probable reason for observed high adverse drug reaction withdrawal was possibly the concern for possible adverse effects. Moreover, the study underlined that the data did not demonstrate any evidence of association between phenobarbitone and higher risk of adverse events related to nervous system, second-generation teratogenicity, and behavioral side effects. Importantly, high discontinuation rates due to neurotoxicity of phenobarbitone were observed in studies conducted in developed countries; however, studies in developing countries did not elicit significant neuropsychological toxicity.<sup>1</sup> The same review accounted this discrepancy in tolerability to the dose of phenobarbitone used in these studies which generally is high in developed countries when compared to relatively lower doses used in developing countries. Additionally, the review suggested that pharmacogenetics, genetic influence, and medico social context may affect the threshold of the reported neuropsychological scores.

Despite broad spectrum of action, affordability, and comparative efficiency, the role of phenobarbitone in the management of SE remains largely unexplored. Interestingly, no randomized or observational studies have been undertaken with phenobarbital in patients with SE from the year 2000.<sup>17</sup> Comprehensive, prospective, randomized control studies evaluating the tolerability, efficacy, and outcome of phenobarbitone in the management of SE in various age

### KEY MESSAGES

- ▣ Lower cost of phenobarbitone than any other AED in current use makes it affordable and suitable for use in low- and middle-income countries.
- ▣ Phenobarbitone can be used in children and adult patients with SE after the first-line administration of benzodiazepines.
- ▣ Phenobarbitone has been reported to be highly effective in the management of refractory SE.
- ▣ Caution must be exhibited when administering phenobarbitone for child-bearing women. One needs to be careful and watch for respiratory depression when giving phenobarbitone immediately after giving a benzodiazepine.
- ▣ No randomized or observational studies have been undertaken with phenobarbital in patients with SE from the year 2000.



and socioeconomic conditions is the need of the hour. Given the low-cost advantage of phenobarbitone in comparison to other AEDs, the onus is on developing countries like India to initiate these efforts. As Nimaga et al<sup>18</sup> suitably pointed out that for poor and developing countries, “the choice is not between phenobarbital and a new medicine but between phenobarbital and no treatment at all”.

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# Phenobarbitone in Childhood Epilepsy

Sheffali Gulati

## INTRODUCTION

Phenobarbitone or phenobarbital was the first anti-epileptic drug (AED) used in 1912. Since then in over 100 years of its use, it has continued to be one of the first-line AEDs due to efficacy and being broad spectrum AED.<sup>1</sup> However, its use is declining in developed countries due to concern over its tolerability issues but it is one of the most common used AEDs in developing countries due to cost effectiveness.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Phenobarbitone acts as a  $\gamma$ -aminobutyric acid (GABA) agonist and it binds with GABA<sub>A</sub> receptor and enhances the GABA receptor-mediated inhibition by prolonging the openings of the chloride channels. Phenobarbital also blocks excitatory responses induced by glutamate. Salient pharmacokinetic factors have been enumerated in Table 1.

### Spectrum

It is a board spectrum AED used clinically in neonatal seizures, status epilepticus (SE), focal and generalized tonic-clonic seizures, febrile seizure (continuous prophylaxis), and as add-on in refractory epilepsy.

**Table 1. Salient Pharmacokinetic Properties of Phenobarbitone**

Pharmacokinetics	Value
Bioavailability	>95%
Target plasma concentration	10–40 µg/mL
Elimination half-life	72–144 h (adults) 59–400 h (newborns) 36–60 h (children)
Route of elimination	Primary hepatic metabolism, 25% renal excretion unchanged
Standard maintenance dose	Children 4–8 mg/kg/day Adults 60–240 mg/day
Daily doses	1–2 divided doses

Modified and adapted from: Kwan P, Brodie JM. *Epilepsia* 2004;45:1141–9.

### Phenobarbitone in Childhood Epilepsy

- The available literature is insufficient to provide level A or B evidence about phenobarbitone use in childhood epilepsy (see the Annexure for level of evidence, source The International League Against Epilepsy [ILAE] Task Force 2013).
- Phenobarbitone is graded as possibly effective or efficacious as initial monotherapy (level C) in children with focal onset of seizures, generalized tonic and clonic seizures.<sup>3</sup>
- Phenobarbitone may aggravate or precipitate absence seizures (level F) (ILAE 2013).<sup>2</sup>
- In children with refractory focal epilepsy, phenobarbitone can be considered add-on therapy by a tertiary epilepsy specialist after use of first-line AEDs and adjunctive AEDs (National Institute for Clinical Excellence [NICE] 2012).<sup>4</sup>

## Annexure

Level of Evidence (where applicable in this document) (Source ILAE)	
Level of evidence	Interpretation
A	AED established as initial monotherapy
B	AED probably efficacious or effective as initial monotherapy
C	AED possibly efficacious or effective as initial monotherapy
D	AED potentially efficacious or effective as initial monotherapy
E	No data available to assess if AED is effective as initial monotherapy
F	AED established as ineffective or significant risk of seizure aggravation

AED: anti-epileptic drug.

### Phenobarbitone in Neonatal Seizures

- ▣ Phenobarbital should be used as the first-line agent for treatment of neonatal seizures.

*Recommendation strength: Strong; Quality of evidence: Very low*  
World Health Organization 2011<sup>5</sup>

- ▣ In neonates with birth asphyxia, prophylactic usage of phenobarbitone is not recommended.

### Phenobarbitone in Febrile Seizures

- ▣ Prophylactic treatment with intermittent antipyretics, intermittent anticonvulsant (diazepam or clobazam), or continuous anticonvulsant (phenobarbitone or valproic acid) should not be considered for simple febrile seizures.

*Recommendation strength: Standard*  
World Health Organization 2012 updated

- ▣ Phenobarbitone may be effective at reducing febrile seizure recurrence in children with a history of simple or complex febrile seizures with risk of behavioral problems such as hyperactivity, irritability, aggression, and cognitive impairment.<sup>6,7</sup>

- ▣ Intermittent diazepam or continuous phenobarbitone may be no more effective at reducing the risk of subsequent epilepsy in children with febrile seizures.<sup>6,7</sup>
- ▣ The evidence is inconclusive whether phenobarbitone is more effective than sodium valproate (VPA) at reducing the proportion of children with febrile seizure recurrence.<sup>7</sup>

### Phenobarbitone in Status Epilepticus

- ▣ Most guidelines mention the use of phenobarbitone or phenytoin (PHT) as a second-line agent after benzodiazepines in treatment of convulsive SE in children and after glucose and calcium in neonates (NICE 2012, ILAE 2013).<sup>3,4</sup>
- ▣ In management of refractory status epilepticus in children, many anecdotal case reports and case series (but no single randomized controlled trial [RCT]) are available stating successful usage of very high dose phenobarbitone.
- ▣ **Advisory board/group recommendations:** After loading 20 mg/kg, 5–10 mg/kg was added every 30 min to 1 h (max cumulatively given in 24 h is 120 mg/kg) till clinical seizures stop or burst suppression achieved in electroencephalography (EEG). Maintenance dose exceeding 10 mg/kg/day is required for median of 7–12 days.<sup>8,9</sup>

### PHENOBARBITONE AND NEUROBEHAVIORAL SIDE-EFFECT PROFILE (TABLE 2)

- ▣ Up to three-fourth children with epilepsy have some form of behavioral problem and a quarter have intellectual disability.<sup>10</sup> Although phenobarbitone demonstrates overall tolerability similar to that of other established AEDs, and serious systemic side effects are uncommon, its potential for neurobehavioral toxicity remains a topic of major concern.
- ▣ These concerns were raised by studies performed in the 1970s and 1980s claiming excessive behavioral side effects and they had negative impact on prescribing behavior specially in developed countries.<sup>11</sup>
- ▣ In a systematic review by Pal,<sup>1</sup> it was concluded that no convincing evidence exists for an excess of behavioral adverse effects, over other AEDs, attributable to phenobarbitone. The trials were

divided into two major groups studying phenobarbitone in febrile seizures and childhood epilepsy.

### Febrile Seizures

Eleven trials on febrile seizures (5 masked, 6 unmasked), with varying degree of follow-up and compared to other intermittent or continuous AEDs or placebo, are reviewed, out of which 1 masked and 2 unmasked trials showed significant behavior disturbances in children as compared to placebo or other AEDs.<sup>1</sup>

### Childhood Epilepsy

- ❑ Nine RCTs (4 masked, 5 unmasked) were studied by the author in childhood epilepsy comparing phenobarbitone with other AEDs.
- ❑ Out of 9 trials in childhood, 2 unmasked trials had reported excess of behavioral problems in study group due to phenobarbitone.
- ❑ The author reported that lack of randomization and validated instruments to report behavioral side effects are the major concerns with these studies.<sup>1</sup>
- ▣ The recent randomized comparison between phenobarbitone and carbamazepine (CBZ) in 108 children in Bangladesh with partial and/or generalized tonic-clonic seizures was with 12 months of follow-up. The authors concluded that there was no excess behavior side effects noted with phenobarbitone administration in resource-limited settings.<sup>12</sup>

**Table 2. Side-effect Profile of Phenobarbitone<sup>2</sup>**

Relatively common	Uncommon
Neurobehavioral <ul style="list-style-type: none"> <li>• Sedation</li> <li>• Behavior</li> <li>• Hyperactivity</li> <li>• Changes in mood and affect</li> <li>• Adverse effect on cognition</li> </ul>	<ul style="list-style-type: none"> <li>• Megaloblastic anemia</li> <li>• Osteomalacia</li> <li>• Hepatotoxicity</li> </ul>
Connective tissue disorders <ul style="list-style-type: none"> <li>• Dupuytren's contracture</li> <li>• Frozen shoulder</li> </ul>	<ul style="list-style-type: none"> <li>• Aggravation of porphyria</li> <li>• Hypersensitivity</li> <li>• Teratogenicity</li> </ul>

Modified and adapted from: Kwan P, Brodie JM. *Epilepsia* 2004;45:1141–9.

## PHENOBARBITONE AND DEVELOPED VERSUS DEVELOPING WORLDS

- High discontinuation rates due to neurobehavioral toxicity have been observed in studies conducted in developed countries, whereas the drug did not show similar neurobehavioral toxicity when used in the developing world.<sup>2</sup>
- This paradox can be explained by the following points:
  - With limited availability of treatment options, patients (and caregivers) in developing countries with untreated epilepsy and associated disability have better acceptance to the neurobehavioral side effects. They perceive benefit from the success in seizure control.
  - Other than efficacy, economic affordability, social acceptability, and availability are major deciding factors in selecting AED in the developing world.
  - The scope of pharmacogenomics on the efficacy and adverse effects is understudied in different populations.

## Controversy

- Recently, one large retrospective study of 280 newborns with comparable seizure etiology and cranial imaging showed worse Bayley Scales of Infant Development (BSID) cognitive and motor scores in those who received phenobarbitone compared to those who were given levetiracetam. They showed statistically significant decrease of 8 and 9 points in BSID cognitive and motor scores, respectively, with 100 mg/kg phenobarbitone while nonsignificant reduction of 2.2 and 2.6 points in respective BSID cognitive and motor scores with 300 mg/kg levetiracetam. The study concluded that cerebral palsy (CP) probability increased by 2.3 fold per 100 mg/kg phenobarbitone and was not associated with increasing levetiracetam.<sup>13</sup>
- In 2013 Cochrane review over phenobarbitone versus PHT monotherapy for partial onset seizures and generalized onset tonic-clonic seizures, the authors have concluded that in terms of seizure control, PHT and phenobarbitone are comparable but studies showed that PHT is less likely to be withdrawn compared to phenobarbitone presumably due to side effects. But lack of masked studies and other biases are major confounding factors for this seemingly preference.<sup>14</sup>



- Phenobarbitone is equally effective and safe as far as common epilepsies are concerned and cognitive scores and mood ratings are comparable in patients taking phenobarbitone monotherapy with age-, sex-, and education-matched healthy controls which is demonstrated by the project study in rural settings of China known as “China Project” (in collaboration with WHO, ILAE, IBE [International Bureau for Epilepsy]).<sup>11</sup> Between December 2000 and June 2004, a total of 2,455 patients were treated. At 24 months of treatment, 71% of patients showed significant benefit, with 26% free from convulsive seizure during the entire treatment period and another 45% having >50% reduction in seizure frequency and the remarkably treatment gap reduction was achieved nearly around 50%. These figures showed efficacy and safety of phenobarbitone as monotherapy.
- A study conducted in rural south India by Mani et al enrolled only 135 patients with generalized tonic-clonic seizures. Fifty-five percent (n = 75) took phenobarbitone, mostly (n = 68) as monotherapy. More than 50% of patients taking phenobarbitone were seizure free at 1 year, but this dropped to 20% over the next 4 years. There were major adverse events in only 3 patients taking phenobarbitone. This study also showed efficacy of phenobarbitone with better tolerability.<sup>15</sup>

### FUTURE IN THE SECOND CENTURY

- Current evidence is supporting phenobarbitone as one of the cost-effective pharmacologic treatments for epilepsy.
- Although there is concern regarding its cognitive side-effect profile which is mainly attributed to poor quality trials, there is need to address this issue with well-designed multicentric large studies.
- Phenobarbital has a large scope to fill the treatment gap in middle-low income countries during its second century of clinical use.

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# Phenobarbitone: Current Status in the Developing and the Developed Countries

Suvasini Sharma

## INTRODUCTION

Phenobarbitone was identified as an anti-epileptic drug (AED) in 1912, and has been in use for more than 100 years now. Its low cost and favorable cost-efficacy ratio, which is lower than any other AED in current use, makes the drug particularly suitable for use in the low- and middle-income countries.<sup>1</sup> *The World Health Organization (WHO) recommends phenobarbitone as a first-line treatment for convulsive seizures in resource-poor countries and includes it in its Essential Drug List.*<sup>2</sup> However, concerns regarding cognitive and behavioral side effects especially in children have largely limited the use of phenobarbitone in the developed world. In this chapter, a brief review of the current role of phenobarbitone in the treatment of epilepsy in the developing versus the developed world is presented.

## EFFICACY

Phenobarbitone is effective for partial and generalized tonic-clonic seizures. In the absence of good-quality randomized controlled trials (RCTs) and recent studies, from the older evidence available, phenobarbitone appears to be at least as effective against both generalized and partial onset seizures as the other standard AED, and most of the newer AED.<sup>3</sup> It is effective against a variety of seizure types. *Absence seizures however do not respond to phenobarbitone and may be aggravated.*<sup>4</sup> Unlike the sodium channel blockers (phenytoin [PHT] and carbamazepine [CBZ]), phenobarbitone does not aggravate primary generalized epilepsy and hence may not require EEG confirmation before starting treatment.<sup>3</sup> It has also been found useful in the treatment of juvenile myoclonic epilepsy.<sup>3</sup>

Recent studies have evaluated the use of phenobarbitone in resource-constrained settings. Nimaga et al, in a study from Mali, reported that phenobarbitone prevented seizure recurrence in about 80% of individuals and reduced the frequency of seizures in

16%.<sup>5</sup> In a large study from rural China (China Project), 68% of the 1897 patients who completed 12 months' treatment with phenobarbitone experienced a substantial reduction in seizure frequency and 34% stopped having seizures altogether.<sup>6</sup> In a recent study from Bangladesh, 108 children aged 2–15 years were randomized to receive either phenobarbitone or CBZ.<sup>7</sup> There were no important differences in efficacy between the drugs over the 12-month follow-up period. Similar results have been obtained in studies from Cameroon, Nigeria, and Laos.<sup>8</sup>

The Yelandur study in Karnataka by Mani et al recruited 135 patients in a nonrandomized trial of PHT and/or phenobarbitone with a 5-year follow-up.<sup>9</sup> More than 50% of patients taking phenobarbitone were seizure free at 1 year. Only 3 (4%) of phenobarbitone-treated patients developed adverse effects. In a RCT of phenobarbitone versus PHT in children from rural India, there was no significant difference in efficacy between the two drugs.<sup>10</sup>

### ADVERSE EFFECT PROFILE

The major concern with the use of phenobarbitone is the *development of cognitive and behavioral side effects (e.g., hyperactivity), especially in children*. These concerns rose in the 1970s and 1980s when phenobarbitone was routinely used for the prophylaxis of febrile seizures in young children. However, careful evaluation of the RCTs from that era does not provide convincing evidence for an excess of behavioral adverse effects, compared to other AEDs. In a systematic review by Pal et al, none of the 9 masked clinical trials of phenobarbitone, for either the prevention of febrile seizures or of epilepsy, has shown an excess of behavioral adverse effects over placebo or active treatment.<sup>11</sup> In comparison, 3 of 11 unmasked clinical trials have attributed significant behavioral adverse effects to phenobarbitone. The lack of randomization and blinding makes selection and observer bias very likely. Nevertheless, these studies were influential in markedly restricting the use of phenobarbitone in children in the developed countries after the early 1990s.

Recent evidence with well-designed studies however demonstrates that phenobarbitone may have a favorable neurobehavioral profile both in adults and children. In the earlier mentioned randomized trial of phenobarbitone versus PHT in children from rural India, the behavioral side effects were assessed using behavioral rating scales such as Conner's scale by investigators masked to the treatment

allocation.<sup>10</sup> The scores on the behavior rating scales did not differ significantly between the phenobarbitone and PHT groups. In a study from rural China by Ding et al, 144 patients were compared with epilepsy with matched controls from villages in China where scores actually improved on retesting after treatment.<sup>12</sup> The most recent evidence has come from a multicentric study from India by Satischandra et al on the effect of phenobarbitone on cognition in adult patients with new onset epilepsy.<sup>13</sup> Seventy-five patients with epilepsy were prescribed phenobarbitone and underwent serial standardized neuropsychological assessment at baseline, 1 month, 3 months, 6 months, and 12 months. There was no deterioration (rather an improvement) during the follow visits in all the neuropsychological functions.

### ROLE OF PHENOBARBITONE IN THE DEVELOPING COUNTRIES

Epilepsy affects more than 60 million people worldwide, and over 80% of them live in resource-poor countries.<sup>14</sup> Approximately, 85% of these people do not receive appropriate treatment because of economic, cultural, social, and legislative barriers.<sup>1,15</sup> The treatment gap in epilepsy in India varies from 40% in Kerala to 90% in West Bengal.<sup>16</sup> Untreated people with epilepsy (PWE) face devastating social consequences, including stigma and discrimination, and risk of death.<sup>1</sup> There is a need for an effective, affordable, and acceptable AED to reduce this treatment gap. Phenobarbitone is most suited for this role. *It has good efficacy, broad spectrum of action, unique mechanism of action, and recent evidence has demonstrated a favorable cognitive-behavioral profile.*<sup>8</sup> Another advantage is its long half-life which permits once-daily dosing, with better likelihood of compliance. The overwhelming advantage of phenobarbitone is its low cost; it is the most cost-effective anti-epileptic medication available.<sup>17</sup> *The World Health Organization (WHO) recommends phenobarbitone as a first-line treatment for convulsive seizures in resource-poor countries and includes it in its Essential Drug List.*

Access to phenobarbitone may be problematic in many developing countries because of controlled drug regulations. *Phenobarbitone, which is listed as a psychotropic substance by the International Narcotics Control Board, is subject to strong international control and to stringent regulations.*<sup>1,18</sup> Access is also limited by inefficient manufacturing, marketing, and central distribution policies more than by restricted prescription, and in many resource-poor countries, the drug can easily be acquired without prescription.<sup>18</sup> Recognizing this, the WHO

*has initiated an Access to Controlled Medication Program that aims, while raising awareness to the potentials of abuse, at modifying the local policies.*<sup>18</sup>

## **ROLE OF PHENOBARBITONE IN THE DEVELOPED COUNTRIES**

Phenobarbitone is much lesser used in the developed world for the following reasons: the unacceptable side-effect profile, the lack of any marketing support (in the face of huge marketing budgets for other compounds), the controlled drug regulations, and anxiety about dependency and addiction, despite the evidence that these risks are slight.<sup>18</sup> It is probable that the negative reputation of phenobarbitone regarding tolerability comes more from its lack of a commercial sponsor than from a critical analysis of the available literature.<sup>18,19</sup> In this respect, phenobarbitone has been said to be suffering from 'commercial neglect'.<sup>19</sup> As of the present, phenobarbitone is mainly used for neonatal seizures, refractory status epilepticus (SE), and as a second- or third-line drug in refractory epilepsy. In a recent study of successful combination therapies from Glasgow, United Kingdom, phenobarbitone together with PHT and CBZ were the 3rd and 9th most common successful duotherapies, respectively.<sup>18,20</sup> The lack of research interest in phenobarbitone can be gauged from the fact that even though phenobarbitone has demonstrated efficacy equal to lorazepam and better than PHT in SE, it has not been considered for evaluation in the much awaited ESET trial of established SE (benzodiazepine refractory SE), in which fosphenytoin, valproate, and levetiracetam will be compared to each other.<sup>21</sup>

## **CONCLUSION**

Phenobarbitone is the most cost-effective treatment for epilepsy. It is a broad spectrum agent with good efficacy. The severity of the adverse effect profile is controversial, and recent evidence suggests that it may be better tolerated than suggested by the earlier studies. Research is needed to evaluate its optimal role in the treatment of refractory epilepsy and SE.

## KEY MESSAGES AND RECOMMENDATIONS

- ▣ Phenobarbitone is the most cost-effective treatment for epilepsy.
- ▣ It is a broad spectrum agent effective against all types of seizures except absence seizures.
- ▣ It has good efficacy.
- ▣ The WHO recommends phenobarbitone as a first-line treatment for convulsive seizures in resource-poor countries.
- ▣ Phenobarbitone is included in the WHO Essential Drug List.
- ▣ The major concern with the use of phenobarbitone is the development of cognitive and behavioral side effects (e.g., hyperactivity), especially in children.
- ▣ Careful evaluation of the RCTs does not provide convincing evidence for an excess of behavioral adverse effects, compared to other AEDs.
- ▣ In children, phenobarbitone is used as the drug of choice in neonatal seizures.
- ▣ In adults, phenobarbitone may be used as a first-line drug in resource-poor settings. In other scenarios, phenobarbitone may be a reasonable second- or third-line drug.

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# Pharmacoeconomics

**Sangeeta Ravat**

Economic evaluation of pharmaceutical products, or pharmacoeconomics, is a rapidly growing area of research. Pharmacoeconomic evaluation is important in helping clinicians and decision makers to make choices about new pharmaceutical products and in helping patients obtain access to new medicines.

The pharmacoeconomic reports shall be used as scientific tools to help decision makers in making informed and rational choices in striving to maximize total health benefits within the budget limitations.

## **TYPES OF PHARMACOECONOMIC ANALYSIS**

There are 4 main types of pharmacoeconomic evaluations:

- ▣ Cost-minimization analysis (CMA)
- ▣ Cost-effectiveness analysis (CEA)
- ▣ Cost-utility analysis (CUA)
- ▣ Cost-benefit analysis (CBA)

Full economic evaluation has 2 major components—costs and outcomes of the compared alternatives. The cost component is always measured in monetary unit, while the outcome component can be measured in various ways such as life years saved, case treated, and utility terms. Cost-minimization analysis compares treatment alternatives that yield similar health consequences. Once the health consequences are established to be the same, a CMA would compare all cost between treatments to determine the option with the least cost. Cost-effectiveness analysis compares the relative difference of costs and consequences of different treatment strategies. In CEA, costs are measured in monetary terms and health consequences are measured in natural or physical units. Cost-utility analysis has the same principle as a CEA, but includes measures of the impact

on the quality of life. Cost-utility analysis is often used when both the quantity and quality of life are important. Cost-benefit analysis compares treatment alternatives where both costs and benefits are expressed in monetary terms.

### ECONOMIC FACTORS OF PHENOBARBITONE

The economic burden due to epilepsy is not adequately examined in developing countries. Cost estimates are very important in healthcare planning and delivery of services. Among the anti-epileptic drugs (AEDs) we have in the market, the greatest advantage of phenobarbitone is its low cost, which in fact is its disadvantage as well, the reason being because of the low cost and less profits, not many pharmaceutical companies actively pursue its production. This is one of the major reasons for the on-going disappearance of phenobarbitone from the clinical scenes of most western countries. In randomized controlled trials (RCTs), no differences in efficacy have been found between phenobarbitone and phenytoin (PHT), carbamazepine (CBZ), or valproate (VPA). There are a few problems with phenobarbitone such as cognition which can be taken care of after dose titration. Few studies have evaluated these economic aspects. In Mali, 1000 tablets of phenobarbitone 100 mg cost \$7.12 and each patient required an average of 1.1 tablets per day i.e., 401.5 tablets per year, or US\$2.56/patient/year, which is far less than the transport costs for physician visits and delivery of supplies to the patients in the villages (~\$915 for 100 patients/year).<sup>1</sup> There are in fact numerous biases inherent in this study. In a recent survey in Cambodia, it is seen that the annual treatment cost is \$4.6 for phenobarbitone (390.5 tablets yearly) and \$8.3 for VPA (333.6 tablets yearly). In India, it is estimated that the cost of PHT is 160% more, of CBZ is 470% more, and of VPA is 530% more than the respective cost of phenobarbitone. For newer AEDs, the cost differences are even more staggering. In Cambodia, it was noted that VPA would cost nearly double of the cost of phenobarbitone, but would also require consuming lesser number of VPA tablets as well.<sup>2</sup>

The defined daily dose for each AED was adjusted for the Indian population (*with prevailing market price in INR*) as follows:

- ▣ Phenobarbitone, 90 mg (1.32);
- ▣ Phenytoin (PHT), 300 mg (2.45);
- ▣ Carbamazepine (CBZ), 600 mg (3.8);

- ▣ Sodium valproate (VPA), 800 mg (8.14);
- ▣ Primidone (PRM), 500 mg (4.75);
- ▣ Clonazepam (CLZ), 2 mg (6.87);
- ▣ Clobazam (CLB), 10 mg (4.8); and
- ▣ Gabapentin (GBP), 400 mg (40).<sup>3</sup>

The annual direct cost related to diagnostic work was derived by dividing the lifetime cost under this head by the mean duration of treatment in years. Travel expense was taken as second-class train fare (INR 60) for the distance from the residence to the clinic (mean 70 km) and daily incidental expense (INR 15) per head.<sup>4</sup>

There is more frequent use of relatively expensive drugs such as CBZ and VPA and the use of polytherapy—still quite prevalent in developing countries—has escalated the cost of AED therapy in a place like India. Widespread use of phenobarbitone has been encouraged in developing countries because of its efficacy for a wide range of seizure types and its low cost.

To conclude, phenobarbitone has been underutilized in the developing countries. The current recommendation by the World Health Organization is that it should be offered as the first option for therapy for convulsive epilepsy in adults and children if availability can be ensured. Phenobarbitone is still considered a first-line treatment in idiopathic (genetic) generalized epilepsy in many areas of the world due to its low cost and ease of use.

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# Indian Consensus Statement— Conclusion

**Man Mohan Mehndiratta**

Though phenobarbitone is more than a century old drug, it still lives in discussions on various national and international platforms because of its relatively broad spectrum and reasonable cost.

The Indian Epilepsy Society has the Guidelines in the Management of Epilepsy in India (GEMIND) where phenobarbitone is mentioned as a first-line drug in the management of all types of epilepsy other than absence seizures. This manual is available on our website [www.epilepsyindia.org](http://www.epilepsyindia.org) as well as on [www.ilae.org](http://www.ilae.org). These guidelines were first from an Asian country and are being utilized by many other Asian countries for clinical practice.

The phenobarbitone guidelines were a long-felt need. Phenobarbitone has a broad spectrum action in epilepsy, efficacy comparable with many newer anti-epileptic drugs and acceptable safety profile and it remains today as the first-line therapy in benzodiazepine-resistant status epilepticus. Low cost is not just phenobarbitone's greatest asset but also greatest liability having led the drug into commercial neglect. Phenobarbitone is recommended by the World Health Organization (WHO) as first-line anti-epileptic drug for partial and generalized tonic-clonic seizures for developing countries. The role of phenobarbitone as drug of choice in neonatal seizures is the outcome of clinical experience.

This document has carefully collated all the information available on phenobarbitone to summarize the current status of phenobarbitone in the management of epilepsy.

A grateful thanks to all the members of the group involved in this endeavor to take out time from their busy schedule to prepare the consensus statement.