Critical Review on Medhya Drugs as an Adjuvant to Overcome Adverse Effect of Long Term Use of Anticonvulsant Drugs in Children

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Abstract

Cognition is the mental process which incorporates memory, calculation, understanding and making dialect, reasoning, attention of operating, problem solving and higher cognitive process. High-quality kid development centres within the world have placed priority on children's intellectual learning.

The rates of unfavourable impacts could be a basic issue while endorsing antiepileptic medicinal drug (AED’s), as a large portion of the anticonvulsant drug have unfriendly impact on psychological feature of youngsters.

Present paper is an audit to overhaul learning on range of adverse effects on psychological feature coupled to a range of newer and older anticonvulsant medication used to control seizures, trailed by a discussion relating to medhal buddhi (intellect), medhyarasayana and use of Ayurvedic medhya dravya to minimize adverse drug reactions (ADR’s), major chemical constituents, therapeutic actions, pharmacologic properties, and doable mode of action of the chosen herbs from Ayurvedic literature. At the same time, it conjointly reveal for additional analysis and use of medhya rasayana (nootropic herbs) as an adjuvant therapy to minimize or conquer adverse impact of long run use of antiepileptic medication in kids.

Keywords

Cognition, Antiepileptic drugs, Medhya rasayana & Adverse effect
INTRODUCTION

Intelligence is the discriminative capability of an individual that makes him completely different from animals. Language, observations, analytical mind, analysis ability and plenty of additional contributed for human intellect. For the successful survival of man during this competitive world there's a desire for promotion of mental state. It becomes invariably essential to own nice skills in terms of memory and intelligence right from the childhood itself. There is a robust affiliation between the event a baby undergoes early in life and the level of success that the kid can expertise later in life. Here development is especially concerned with psychological development of a baby. Epilepsy is a common disorder in medicine practice that demands usually long term medical care. There are only a few medicine studies relating to incidence of epilepsy from India. A recent study conducted in Kolkata's urban population showed an annual incidence rate of 27.27 per 100,000 per year\(^1\). A recent rural epilepsy surveillance program from Uttarakhand showed a prevalence rate of 2 or more unprovoked seizures to be 7.5 per 1000\(^2\). This can be more than the prevalence rate in Kerala, whereby prevalence rate is 4.9/1000\(^3\).

The ultimate aim in treating epilepsy ought to be complete management of seizures, while not inflicting any untoward reaction as a result of the medication. A large variety of drugs are presently on the market for the treatment of epilepsy. Effective treatment of epilepsy depends on medication compliance across a time period, and studies indicate that drug tolerability could be important limiting factor in medication maintenance. Available anticonvulsant medication (AED’s) have the potential to exert harmful effects on psychological feature operate and thus compromise patient wellbeing.

Antiepileptic medication decrease membrane excitability, increase postsynaptic inhibition or alter synchronization of neural networks to decrease excessive neuronal excitability related to seizure development. Common side effects of decreasing neuronal excitability, however, are slowed motor and activity speed, poorer attention and mild memory impairment\(^4\) (Meador, 2005). Unlike adults, psychological side effects in children occur against the scene of normal cognitive and psychosocial development, and treatment decisions made in childhood might have long effects. Adults who
developed epilepsy during their childhood tend to own less education, ablated rates of employment and employment at lower job levels, lower rates of wedding, poorer physical health, and enhanced incidence of psychiatric disorders. Significantly, these long term adverse effects are present in adults who aren't any longer taking medications. The persistence of those effects when termination of AED treatment suggests a role of either seizure etiology, accumulative effects of continual seizures or AED treatment permanently altering the course of development.

Ayurveda has its own principle which may prove an excellent answer for several of the issues involved with mind and body. The description concerning the construct of Medhya Rasayana is one such idea which needs reconsideration and application in present situation because it may be a robust answer for several of the psychological and cognitive issues.

**MATERIALS AND METHODS**

In this current literature, we reviewed studies in terms of range of effects on cognition connected to a range of newer and older agents used to control seizures (Table no.1). These embody key alterations in both executive and broader neuropsychological functions, which may exert essential influence on children’s quality of life and well-being. As a result of drug side-effect profiles are typically associated with patient characteristics, this review is followed by an essential discussion concerning idea of medha, medhyarasayana and use of Ayurvedic medication to minimize ADR’s, which can provide recommendations for prescribing medication each in general and in respect to a lot of specific clinical cases.

Finally, we valuate reviewed studies in terms of knowledge improving actions, toxicity, interaction of Ayurvedic medication, providing essential steerage for using it in clinical practice.

Cognitive deficits that are secondary to adverse effect of many of antiepileptic drugs (as explained in table no 1) demand use of medhya dravya (nootropics) to boost cognitive abilities. Recently there is a tremendous urge to explore medicinal plants on global platform for improving cognitive function owing to their less adverse effects. Ayurveda provides concept of medhya rasayana to boost up the cognition of an individual.
CONCEPT OF MEDHA AND MEDHYARASAYANA

In different Sanskrit/English dictionaries following terms are used for medha-
A form of Saraswati, retentive faculty/retentiveness of memory, intellect, and intelligence in general, strength, mental power or vigor, prudence, wisdom and intelligence personified.

Medha is considered as a form of buddhi itself. Buddhi is a functional unit of human body which perceives the stimulus either from sense organs or from memory and imaginations. The man with proper buddhi gets proper impulses from the interior or exterior world and buddhi gets involved with indriyas and manas and perceives the knowledge.

Measures to improve medha

There are many methods by which medha can be manipulated. Some methods are concerned with the maintenance of equilibrium status of body and mind, there by facilitating the normal physical and psychological functions. Some other measures are directly acting on the psychological entities by which medha can be improved.

Specific Measures

Treatment modalities according to Ayurveda can be explained as- Svasthasyaurjaskara & arthasyaroganut.

Urjaskarachikitsa is mainly concerned with preventive and promotive medicine where arroganut deals with curative therapy. Rasayana and Vajeekarana are the two forms of Urjaskarachikitsa. Though Rasayana is one among the eight branches of Ayurveda, it has its applicability in all the branches of Ayurveda. Rasayana is the most applied specialty of Ayurveda.

Use of medhyarasayananas is specifically meant for improving the medha. Charaka samhita mentions about four medhyarasayananas as mandukaparni, yashtimadhu, guduchi and shankhapushpi.

Sushruta Samhita mentions in detail about medhayushkameeyarasayanas.

In Kashyapa Samhita there is mentioning of preparations such as Brahmighrita Panchagavyaghrita Kalyanakaghrita and Samvardhanalehya having medhya effect. Commonly indicated drugs for Cognition improvement in Ayurveda classics with their active ingredients are explained in Table no 2.
**Table 1** Commonly used AED’s (Anti-epileptic drugs) with their cognitive adverse effects (CAEs)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of drug</th>
<th>cognitive adverse effects (CAEs)</th>
<th>References</th>
</tr>
</thead>
</table>
| 1       | Phenobarbital| lower IQ\(^{7}\), more adverse effects on motor performance and attention/concentration tests\(^{7}\), attentional and memory difficulties\(^{8}\) impaired attention\(^{9}\). | 6- Farewell et al. 1990  
7- Smith et al. 1987  
8- Riva and Devoti 1996  
9- Mannie et al. 1993 |
| 2       | Phenytoin     | Poor concentration, memory, visuomotor functions and mental speed\(^{10}\) more detrimental effects on memory than carbamazepine\(^{10}\) slowed performance on information processing tasks with phenytoin in comparison with carbamazepine\(^{11}\). | 10- Pulliainen and Jokelaenen, 1995;  
11- Aldenkamp et al. 1994 |
| 3       | Carbamazepine | deterioration in measures of information processing speed and attention,\(^{12}\) detrimental effects on memory,\(^{13}\) worse arithmetic performance\(^{14}\). | 12- Wesnes et al. 2009  
13- Shehata et al. 2009  
14- Kang et al. 2007 |
| 4       | Sodium valproate and ethosuximide | detrimental impact on cognitive function,\(^{15}\) subtle changes in cognitive function,\(^{16}\) relationship between plasma concentration and cognitive performance in children\(^{17}\). | 15- Sun et al. 2008  
16- Prevey et al. 1996  
17- Brouwer et al 1992 |
| 5       | Topiramate    | impaired concentration,\(^{18}\) cognitive dulling,\(^{19}\) psychomotor slowing,\(^{20}\) detrimental effects on short-term memory\(^{21}\) reduced IQ score\(^{22}\). | 18- Froscher et al. 2005  
19- Coppola et al. 2008  
20- Tatum et al. 2001  
21- Gomar et al. 2007  
22- Sun et al. 2008 |

**Table 2** Common drugs indicated for Cognition improvement in Ayurveda classics with their active ingredients

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Drug</th>
<th>Classical Indication(^{28,30})</th>
<th>Active ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shankhapushpi</td>
<td>Kalka (fine paste) of whole plant highly regarded as Medhya</td>
<td>Microphyllic acid, shankhapushpin, kaempferol &amp; its glucoside, 3, 4 dihydroxydihydroxyaminic acid, sitosterols.</td>
</tr>
<tr>
<td>2</td>
<td>Yashtimadhu</td>
<td>Choorna (fine powder) of dried root is used by oral route with milk for therapeutic purpose as Medhya.</td>
<td>Glycyrrhizine, flavonones, isoflavones, glycyrrhetenic acid, many phenolic compounds.</td>
</tr>
<tr>
<td>3</td>
<td>Brahmi</td>
<td>whole plant juice is recommended for increasing Medha (intellect)</td>
<td>Saponin, jujubogenin, bacopasaponin G, and glycoside, bacopasides III, IV and V</td>
</tr>
<tr>
<td>4</td>
<td>Guduchi</td>
<td>Swaras (Juice) of whole plant is used therapeutically as Medhya.</td>
<td>Alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides.</td>
</tr>
<tr>
<td>5</td>
<td>Mandukparni</td>
<td>Swaras (fresh whole plant juice) is used for therapeutic purposes as Medhya (cognitive enhancer)</td>
<td>Saponin (medacoside, asiaticoside, medacassoside, asiatic acid &amp; triterpenic acid.</td>
</tr>
<tr>
<td>6</td>
<td>Jatamansi</td>
<td>Rhizome is used for medicinal purposes in different psychiatric illness as it has</td>
<td>Terpenoid ester, nardostachysin I</td>
</tr>
</tbody>
</table>


**Evidences from different researches**

MANDOOKPARNI (Centella Asiatica)

- Mandookparni has shown brain growth promoter activity\(^3^1\).
- Dendritic arborisation activity of mandookparni is supposed to be the neuronal basis for improved learning and memory\(^3^2\).
- Anti-seizure activity of Mandookparni may result from direct or indirect modulation of ATPase activity\(^3^3\).
- Centella asiatica inhibits the memory impairment induced by scopolamine through the inhibition of AChE\(^3^4\).

SHANKHAPUSHPI (Convolvulus pleuricaulis)

- Pre-clinical research on BR-16A (Mentat-polyherbal compound containing shankhapushpi) has established that it enhances cognition and also protects rats against amnesia (anterograde and retrograde amnesia) induced by electroconvulsive shock\(^3^5\).
- **Learning, memory and behavior**\(^3^6\) - The ethanolic extract of shankhapushpi has shown significant improvement in learning and memory in rats using various laboratory models for learning and memory assessment.

- **Anticonvulsant activity** - water soluble portion of ethanolic extract of shankhapushpi decreased spontaneous motor activity and the fighting response. It has also seen that, electrically induced convulsive seizures were antagonized by the extract of Shankhpushpi\(^3^7\).

Animals treated with the methanolic extracts of whole plant of shankhapushpi, showed significant protection against tonic seizures induced by transcorneal electroshock, which was comparable with that of standard drug phenytoin\(^3^8\).

YASHTIMADHU (Glycyrrhiza glabra)

- The roots and rhizomes of Yashtimadhu (Glycyrrhiza glabra) is an efficient brain tonic; it increases the circulation into the CNS system\(^3^9\).
- Liquorice has shown significant action on memory enhancing activity in dementia. Improved learning and memory on scopolamine induced dementia was observed\(^4^0\).

GUDUCHI (Tinospora Cordifolia)
• *Guduchi (Tinospora cordifolia)* has been claimed to possess learning and memory enhancing activity\(^{41}\).
• *Tinospora cordifolia* enhance the cognition in normal and cognition deficits animals in behavioural test Hebb William maze\(^{42}\).
• Cognitive enhancement mechanism of *Tinospora cordifolia* is by immune stimulation and increasing the synthesis of acetylcholine\(^{43}\).

**BRAHMI (Bacopa Monniera)**
• Brahmi has Cognitive enhancer properties\(^{44}\).
• Alcoholic extract of Brahmi increases cognitive function and retention capacity, decreases retrograde amnesia. Protection from phenytoin -induced cognitive deficit in the Rats was also observed\(^{45}\).
• Brahmi (*Bacopa Monniera*) mainly utilized in the treatment of memory and attention disorders\(^{46}\).

**JATAMAMSI (Nardostachys jatamansi)**
• *Jatamansi* is proven to have effect on improving learning and memory in mice\(^{47}\).
• An acetone extract of *N. jatamansi* has shown significant inhibition of benzoyl peroxide-induced cutaneous oxidative stress in mice\(^{48}\).

• Roots and rhizomes of *N. jatamansi* are used to treat epilepsy, hysteria, and convulsions\(^{49}\).
• The *kwath* (decoction) of the *Jatamansi* is also used in neurological disorders, insomnia and disorders of cardiovascular system\(^{50}\).

**DISCUSSION & CONCLUSION**

Data obtainable thus far support procognitive activity of herbs explained in Samhita within the context of medhya rasayana; at a similar time demand substantial evidences and revalidation in humans. Above aforementioned herbs act on the premise of antioxidant, adaptogenic or essential trace components present in them. Their activity on modulation of biological axis and neurotransmitters needs additional investigation so as to use them as an adjuvant medical aid.

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