

REVIEW ARTICLE

DRUGS INFLUENCING COGNITIVE FUNCTION

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DRUGS INFLUENCING COGNITIVE FUNCTION

Drugs can influence cognitive function in several different ways. The cognitive enhancers or nootropics have become a major issue in drug development during the last decade. Nootropics are defined as drugs that generally increase neuron metabolic activity, improve cognitive and vigilance level and are said to have antidementia effect (1). These drugs are essential for the treatment of geriatric disorders like Alzheimer's which have become one of the major problems socially and medically. Considerable evidence has been gathered in the last decade to support the observation that children with epilepsy have more learning difficulties than age matched controls (2, 3). Anti-epileptic drugs are useful in controlling the frequency and duration of seizures. These drugs can also be the source of side effects including cognitive impairment. Since 1975, greater attention has been given to assess the cognitive effects of anti-epileptic drugs. By learning more about cognitive effects of anti-epileptic drugs, patients can be offered optimal therapy combining excellent seizure control with the least possible negative impact on intellectual functioning. This review is an update on information on drugs which can improve cognitive function as well as those which may produce cognitive dysfunction.

Diseases associated with cognitive impairment : Dementia is characterised by decline in memory, thinking and emotional functions. In the descriptive diagnosis of dementia disorders, different aspects are mentioned; benign senile forgetfulness, primary degenerative disorders, secondary dementias,

cerebrovascular disorders with dementias and reversible dementias.

Primary degenerative disorders include the subgroups senile dementia of the Alzheimer's type (SDAT), Alzheimer's disease, Picks disease and Huntington's chorea (4). Alzheimer's disease usually occurs in individuals past 70 years old and appears to be in part genetically determined (5).

Pathophysiology of Alzheimer's disease : Extensive research in the recent years has made major advances in understanding the pathogenesis of Alzheimer's disease (6). The hallmark lesions of Alzheimer's disease are neuritic plaques and neurofibrillary tangles. Two amyloid proteins accumulate in Alzheimer's disease, these are beta amyloid protein and paired helical filament protein (7). Based on the amyloidoses associated with other diseases, three mechanisms for amyloid formation have emerged. One mechanism involves posttranslational event which render a normal protein amyloidogenic. Proteolysis, phosphorylation, glycosylation and transglutamination may be the relevant, posttranslational events in Alzheimer's disease, another mechanism for amyloid formation results from expression of an abnormal gene which in the case of familial Alzheimer's disease may be an important etiological component. A third mechanism involves the accumulation of a normal protein to a threshold concentration that spontaneously forms amyloid. These mechanisms of amyloid formation can become targets for drug therapy. The number of neuritic plaques and neurofibrillary tangles are positively correlated to

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the severity of clinical symptoms and cognitive impairment.

Neurochemical and neuroendocrine disturbances of Alzheimer's and SDAT have been described by various workers. Olney reported that there is deficiency of the neurotransmitter acetylcholine (8). Autopsy studies have suggested that cholinergic neurons are selectively lost in these disorders. Cerebrospinal fluid concentration of acetylcholine showed good correlation with the degree of cognitive impairment ($r = 0.7$) in a sample of carefully diagnosed patients; but metabolites of other neurotransmitters were not related to cognitive state. This suggest that CSF Ach may be a valid measure of cholinergic degeneration (9). Reduction of choline acetyltransferase activity, a cholinergic marker has been significantly correlated to the severity of dementia (10). Agnoli et al (11) also observed a correlation among the degree of memory loss, intellectual impairment, the quantity of senile plaques, and a decrease in choline acetyltransferase and acetylcholinesterase activity in patients affected by senile dementia of the Alzheimer's type.

The monoaminergic neurotransmission deficit seen in dementia of the Alzheimer's type (DAT) is linked to a known increased activity of type B cerebral monoamine oxidase (12). Drugs that can block this abnormal activity have been found to be useful in the treatment of some cognitive deficits. Postmortem human brain studies have shown a disturbed metabolism of serotonin and overactivity of neuroendocrine controlling factors in the hypothalamus (13). Somatostatin is consistently diminished in brains of patients with Alzheimer's disease (14). Cortisol dysregulation may be a marker for abnormalities in other neurotransmitter systems, particularly the noradrenergic system. Aetiological factors associated with Alzheimer's disease are genetic factors, aluminium or other toxic factors, immunological disturbances, disturbed glucose metabolism, deficiency of essential nutrients and stress.

ANIMALS MODELS FOR LABORATORY EVALUATION OF COGNITIVE FUNCTION

A. Learning and memory

The changes in learning and memory has been,

studied in rats and mice by various workers. Passive avoidance with punishment reinforcement termed as step-through method, and two-way active avoidance with punishment reinforcement known as 'shuttle-box' are reported as useful methods of testing for learning and memory, in these animals (15). Various test drugs have been used in experimental studies to observe their effects on learning and memory. These include nootropics such as piracetam, fipexide, oxiracetam, adafenoxate, meclofenoxate, citicholine, aniracetam, standardised ginseng extract, cholinomimetic compounds like scopolamine, linopirdine, cholinesterase inhibitors such as tacrine, amiridin, physostigmine and drugs influencing monoaminergic neurotransmitter such as MAO inhibitors and 5-HT uptake blockers.

Age related changes on learning and memory has been observed by Burov et al (16). 18 months old rats showed much less learning ability in comparison with that of 3 months old rats. 20 days treatment of old rats with amiridin, tacrine and piracetam improved latency in passive avoidance test to the level of 3 months old rats. Mondadori et al (17) also studied the effects of new compound on age-related cognitive dysfunctions in rats using one way active avoidance situation. Petkov et al (18) used rats of age varying from 2 to 22 months in experiments using active avoidance with punishment reinforcement (maze and shuttle-box and passive avoidance (step-down) to observe age related differences in memory. On their study the nootropics adafenoxate, meclofenoxate, citicholine, aniracetam and the standardised ginseng extract administered orally for 7-10 days usually facilitated learning and improved memory in the rats of all ages. Old rats showed pronounced favourable effects by some of the indices. The biochemical changes observed with aging are decrease in the activity of acetylcholinesterase, reduction of unsaturated fatty acids, the increase of cholesterol content and the increase of microviscosity of membranes of brain synaptosomes. Multiple treatment with amiridin, piracetam and tacrine normalised these indices.

Scopolamine impaired memory has been used by Petkov et al (19) to determine drug effects. In these

experiments scopolamine (2 mg/kg, ip) was used and step-through passive avoidance method was used to determine the memory changes. Test drugs were given for 7 days before training or immediately after training. The test drugs adafenoxate, meclofenoxate, piracetam and citicholine prevented the scopolamine induced retrograde amnesia partially or completely. Lenegre et al (20) used scopolamine, diazepam and electroconvulsive shock to produce amnesia in mice with passive avoidance procedure. Amnesia was induced by injecting scopolamine or diazepam (1 mg/kg, ip), 30 min before the passive avoidance task. Electroconvulsive shock is applied immediately after the first session of the passive avoidance task for producing amnesia. Piracetam when administered in varying doses 60 min before first session attenuated the memory deficits induced by the three amnesic treatments but did not affect either scopolamine induced hyperactivity, diazepam-induced release of punished behaviour or ECS induced convulsions. These results point to the specificity of piracetam's anti-amnesic activity and suggest that piracetam can suppress the memory disturbances without influencing anxiolytic actions of diazepam.

Potassium ethylxanthogenate, the inhibitor of dopamine-beta-hydroxylase, has been used by some workers (21) to induce changes in learning and memory. This compound when injected intraperitoneally in a dose of 100 mg/kg, markedly impaired learning and memory by the active conditional avoidance method with negative reinforcement (shuttle-box) and the passive avoidance method (step-down). Piracetam, aniracetam, meclofenoxate and fipexide administered orally five days before step-down training, completely prevented the impairing effect of potassium ethylxanthogenate on the cognitive processes.

Voronina et al (22) reported on the anti-amnesic action of nicergoline using experimental methods based on passive avoidance responses. Amnesia was induced by maximal electroshock and scopolamine in mice and by paradoxical sleep deprivation in rats. In this study nicergoline demonstrated well-expressed anti-amnesic effect as compared to reference drugs like piracetam and meclofenoxate. Memory-impairing effect of

clonidine has been used by Lazarova, Bakarova and co-workers (23) to observe the influence of nootropics like piracetam, aniracetam, meclofenoxate and fipexide. The changes in learning and memory were studied by two way active avoidance with punishment reinforcement (shuttle-box). Clonidine injected intraperitoneally at a dose of 0.1 mg/kg immediately after a one-day shuttle box training significantly impaired retention. A 5-day treatment before the training session with test drugs completely abolished the memory-impairing effect of clonidine. Sharma and Kulkarni (24) have used elevated plus-maze as the method to evaluate learning and memory mechanisms in rats and mice. Transfer-latency (TL) was used as a parameter for acquisition and retention of memory process on elevated plus-maze in rats and mice. Shortened TL on 2nd day trial in old rats and mice as a parameter for retention or consolidation of memory was reduced by nootropics. The drugs producing acquisition deficits like scopolamine does not show any effect on the retention parameter like the shortened transfer latency.

Exposure to alcohol pre and postnatally is known to influence learning and memory (25). Using conditioned-reflex methods for active and passive avoidance with punishment reinforcement, memory deficit was noted in 12 week old rats exposed perinatally to alcohol. The nootropics piracetam and meclofenoxate administered orally for 5 days before the training session were effective in decreasing memory deficits.

Hypoxia is another stimulus which induces deficits in learning. Behavioural studies with linopirdine have shown that it enhances acquisition of active avoidance and protects against hypoxia induced deficits of passive avoidance in rats. Acquisition of lever pressing for food in native rats is another behavioural model. Linopirdine is reported to enhance performance motivated by foot shock or food as well as behaviour involving active or passive responding (26). The behavioural activities of piracetam and oxiracetam were studied during the learning tests active avoidance, passive avoidances, and T-maze. The levels of the orientation reaction and emotionality of the animals

were determined by the "openfield method. Both nootropics facilitated the learning of the animals, but failed to change their behaviour in the open field.

Animal models for testing antidementia effect specifically : Basal forebrain lesioned rat is one of the widely used animal models for the study of learning impairment (27). Stereotoxic injection of ibotenic acid into the basal forebrain produces marked decrease of acetylcholine as well as cholineacetyl transferase and acetylcholinesterase activities. Cholineacetyl transferase levels are reported to be decreased after 7 days and may return to control values (87%) after 12 weeks. Significant neuronal loss and diminution of size of neurons and decrease of Ache activity are noted in these chronic basal forebrain lesioned rats. However, neurofibrillary tangles or neuritic plaques are not observed.

Learning impairment of the basal forebrain lesioned rats are evaluated by passive avoidance response. Post-training of basal forebrain lesioned rats causes rapid extinction of acquired passive avoidance response (27). Acquisition and retention of learning can be measured using passive avoidance test. Aniracetam given in as dose of 50 mg/kg one hour before the trial has been reported to show an increase in the percentage of conditioned active avoidance responses and a reduction of the latency times (28). This improvement in behavioural performance has been correlated with biochemical studies involving activation of transducing systems in brain such as acetylcholine release and inositol phosphate production in cortical synaptosomes.

Another recent development is related to the advance in technology associated with genetic engineering. Transgenic mice mimicing Alzheimer's pathology have been considered as a suitable model. The germ-line DNA of mice can be manipulated in such a way that the abnormal gene is incorporated in the DNA sequence. The injected DNA becomes integrated into the mouse chromosomal DNA on a fraction of the injected cells. These animals can be used to breed and to obtain transgenic or mutant mouse strains. Unterbeck and colleagues used the APP

(amyloid precursor protein) promoter to express the B/A4 domain of human APP in transgenic mice (6). Transgenic models of cerebral B/A4 amyloidosis should provide powerful tools for assessing the role of B/A4 in Alzheimer's disease.

Biochemical studies : *In vitro* on the effects of drugs like amiridin, tacrine, physostigmine and piracetam were tested on monoamine oxidase A and B activity in the rat brain. Piracetam increased MAO-A and MAO-B activity dose dependently (29). Piracetam also had a potential action in scavenging free radicals. This antioxidation effect may be related to its clinical effects on amnesia and Alzheimer's disease (30). Cholinomimetic and anticholinesterase activity of various compounds have been tested *in vivo* and *in vitro* to determine their effects. Long lasting inhibition of the metabolism of acetylcholine has been attributed to the pharmacological effects of tacrine (31). Cholinergic muscarinic binding capacity of peripheral blood lymphocytes of patients with senile dementia of the Alzheimer's type exhibited a marked reduction in binding capacity. Treatment of these patients with antimuscarinic drugs was associated with increased muscarinic binding by peripheral blood lymphocytes. These results indicate that cholinergic muscarinic binding by peripheral blood lymphocytes may be useful in the study of senile dementia of the Alzheimer's type as well as in evaluating changes induced by certain cholinergic drug treatments. Rat brain slices have been used to study drug effects. Stimulus induced release have been used to study drug effects. Stimulus induced release (K^+ stimulated release) of Ach is useful for the study of drug effects. Receptor binding studies with linopirdine have shown a unique receptor to which it has a specific and exclusive affinity. These receptors are regionally distributed in the same areas as in Alzheimer's. Correlation has been shown between binding and functional effect of stimulus induced release of Ach.

Relationship of steroids to the memory enhancing effects of nootropics and cholinomimetics has been studied in mice by Mondadori et al (32). Elevated steroid levels suppress the memory enhancing effects of these agents. Hausler et al (33) also observed that

adrenalectomy blocks the memory-improving effect of piracetam like compounds in mice. These effects were overcome by replacement with corticosterone or aldosterone given in the drinking fluid. Amnesic syndrome associated with multiple injections of scopolamine resulted in significant deterioration of rats performance in passive avoidance test. Behavioural disorders were accompanied by changes in lipid composition of brain synaptosomes which indicated a decreased membrane fluidity. Amiridin and tacrine as well as piracetam showed anti-amnesic action which correlated with their normalising effect on lipid content of synaptosomes. Electroencephalographic studies have been done in rats to observe the effect of nootropics. Linopirdine is reported to increase relative power in beta waves and decrease relative power in slow waves, thus demonstrating a vigilance pattern.

STUDIES IN HUMAN SUBJECTS ON LEARNING AND MEMORY

Psychometric tests and EEG have been done in elderly patients to test the effect of oxiracetam and piracetam. In one study (34) on 2 subgroups of patients with Alzheimer's disease, piracetam produced a decrease in EEG power and improvement in some psychometric tests. EEG spectral analysis showed good correlation with improvement in some psychometric tests. Studies can be done in human volunteers to test the effects of drugs on memory. Two major classes of studies have been conducted in human subjects; the first is analogous to that dealing with animals and utilises nonverbal material, while the second is concerned with verbal learning. Nonverbal learning may be exemplified by eye-lid and galvanic skin response and salivary conditioning. Another nonverbal form of human learning is found in the development of motor skills such as tracking on a pursuit rotor or automobile-driving (35). Weiss and Laties (36) have reviewed studies reporting enhancement of human performance by caffeine and amphetamine. Danion and co-workers (37) have used verbal tests such as free-recall task, word-completion task and a puzzle test to study the effect of chlorpromazine and lorazepam on explicit memory. Effects of haloperidol has been tested using recall and information processing in verbal and spatial learning by Mungas and co-workers (38).

DRUG THERAPY IN ALZHEIMER'S DISEASE

Drugs may be part of the treatment for Alzheimer's disease. Drug treatment can be divided into two categories, treatment to improve (i) cognitive function (ii) abnormal behaviours. There are atleast 16 new drugs undergoing evaluation that may improve cognitive function. Some of these drugs are intended to augment function of the neurotransmitter acetylcholine. Others are nootropics that improve neuronal function. Drugs which may influence the behaviour in Alzheimer's disease include neuroleptics, anxiolytics and antirage drugs. Another category of drugs useful in this disease state are those drugs that modify other defects such as blood supply to brain (1).

DRUGS IMPROVING CHOLINERGIC FUNCTION

Attempts at pharmacotherapy have been directed towards the enhancement of cholinergic function within the central nervous system. Cholinesterase inhibitors such as physostigmine salicylate, tacrine, amiridin have been used. They are effective in the treatment of cognitive deficits and memory loss associated with senile dementia of the Alzheimer's type (39, 40). Patients with Alzheimer's disease are known to have decreased cell membrane protein-protein interactions. Tacrine reverses this cell membrane defect at least in erythrocytes. Tacrine may have a wider influence on brain function than just as a cholinesterase inhibitor. Velnacrine, a cholinesterase inhibitor and a metabolite of tacrine increased the word and object recognition memory and regional cerebral blood flow in patients with Alzheimer's disease (41). Another drug treatment strategy is to increase acetylcholine precursors in an effort to increase acetylcholine production (42). It may be useful as an adjunct with other drugs. Acetylcholine releasers exemplified by linopirdine (Dup 996) and agents which act as agonists at the various muscarinic subtypes as exemplified by FKS-508 appear to enhance cognitive function in animal models.

NOOTROPICS

The mechanism by which the nootropics affect memory is not known and most of them stimulate phospholipid turnover and protein synthesis and

enhance cholinergic neurotransmission. Piracetam a nootropic in combination with acetylcholine precursors (Eg Lecithin) may have some benefit in a subgroup of patients with Alzheimer's disease, particularly the group with some quantity of remaining functional acetylcholine neurons (43). On long term administration in high doses piracetam may slow the progression of cognitive deterioration in patients with Alzheimer's disease (44). Oxiracetam has been used with success in patients with primary degenerative, multi-infarct or mixed dementia (45, 46). Aniracetam, a new nootropic drug has also been effective in the treatment of dementia of Alzheimer's type.

VASCULAR SYSTEM

The most widely used specific drug treatment for dementia is a compound of ergoloid mesylates (Eg. Hydergine). They decrease vascular resistance and thereby increase cerebral blood flow (47, 48). They increase alertness. Another ergot drug, nicergoline produced an improvement in disorientation in 30% of treated patients (49). Captopril, which is an angiotensin converting enzyme inhibitor may be of use in the treatment of Alzheimer's disease in improving the cognitive function (1).

MISCELLANEOUS NEUROACTIVE DRUGS

Attempts have been made to increase other central neurotransmitters. The most successful has been the use of selegiline (L-deprenyl), a MAO-B inhibitor which increased brain serotonin and nor-epinephrine (50, 51). Sunderland et al (52) focussed on the concept of combination of chemotherapy as a therapeutic strategy. Combination of physostigmine and L-deprenyl have been reported to be more beneficial than either agent alone because of the additive effect of these two drugs (53).

DRUGS AFFECTING BEHAVIOUR

These are grouped into three categories neuroleptics, anxiolytics and antirage drugs. Neuroleptics that are useful in the treatment of patients with dementia are haloperidol, thiothixene hydrochloride (54). Anxiolytics chiefly, benzodiazepines may be useful in treating agitation.

Oxazepam is safer than the long acting benzodiazepines in the treatment of behavioural disturbances in geriatric, psychogeriatric and demented patients (55).

Antirage drugs-propranolol hydrochloride has been useful in treating rage and violent behaviour in demented patients (56, 57). Carbamazepine has been used successfully to treat agitation in dementia (58). Patients with manic episodes may especially benefit from the addition of carbamazepine to haloperidol treatment (59). There are also case reports of successful treatment of aggressive agitations in dementia using the serotonin reuptake blocker fluoxetine hydrochloride (60).

CLINICAL STUDIES

Clinical studies involving phase III programme has been undertaken for linopirdine (Dup 996). E 2020, a new cholinesterase inhibitor with a novel chemical structure has undergone pharmacokinetic study in healthy human subjects. It is generally well tolerated and the pharmacokinetic data suggests dosage regimen of 2 mg once a day. Galanthamine, which is a cholinesterase inhibitor was found to bring a positive change in competence of everyday routine and in the emotional situation in patients with Alzheimer's disease (61). Glebs et al (62) demonstrated the use of huperzine-A, a potent acetylcholinesterase inhibitor in the treatment of Alzheimer's disease. Oral physostigmine, a cholinesterase inhibitor and lecithin, a choline containing phospholipid has been tried in patients with Alzheimer's disease (63). Peak improvement was observed with doses of 2 to 2.5 mg. An inverted U-shaped dose response curve has been found during treatment with intravenous physostigmine for memory impairment, suggesting a narrow therapeutic window response to this drug. Long term continuous infusion of the muscarinic cholinergic agonist arecholine improves the verbal memory in dementia of the Alzheimer's type (64). N - (n-propyl) - N- (4-Pyridinyl) 1 H-indol-1- amine hydrochloride (HP-749, 1) a non-receptor dependent cholinergic agent has been tested for the treatment of Alzheimer's disease (65). Nor-adrenergic intervention alone is unlikely to be effective in Alzheimer's disease (66). A novel compound HP 128 which manifests adrenergic and cholinergic

properties has undergone clinical trials and found to be safe and well tolerated in patients with Alzheimer's disease. It needs further evaluation for its use (67). Clinical trials with cholinergic agents suggest that cholinergic hypertrophy may be beneficial in the treatment of Alzheimer's disease. Recent findings substantiate the view that nerve growth factor (NGF) selectively acts on cholinergic neurons. In animal studies it has been proved that nerve growth factor produces trophic actions on cholinergic neurons and prevents age-related neuronal atrophy suggesting the possibility of the eventual development of pharmacological application of nerve growth factor for the treatment of Alzheimer's disease (68).

Phase I studies have been undertaken by Allain et al (69) using cebaracetam (ZY 15119) in the elderly patients. This compound is reported to act preferentially on memory process. The tolerability of this drug has been tested in young healthy volunteers in phase I studies using increasing doses of 400, 800 and 1600 mg. In a randomized, double blind trial in elderly patients with mild to moderate cognitive impairment for a period of 9 weeks, improvement has been reported in subgroups of patients classified as primary degenerative dementia. Pharmacokinetic studies have been done on cebaracetam in healthy, female volunteers (69). It was well tolerated in both acute and chronic administration and half life after a single dose is about 16 hours. The cognitive enhancing effects of pramiracetam, a nootropic drug in animal models of learning and memory are characterised by an inverted U-shaped dose response curve. The anti-dementia effect of this drug has been evaluated in patients with Alzheimer's disease but the results are inconclusive.

The selective 5-hydroxytryptamine re-uptake blocker, citalopram has proven effective in reducing overactivity on the hypothalamic-pituitary-adrenal axis and in improving emotional disturbances in patients with dementia (70). It produces a significant improvement in emotional bluntness, confusion, irritability, anxiety, fear, panic, depressed mood and no improvement in psychomotor and cognitive behaviour. This drug is considered as an emotional stabilizer (71, 72). Treatment trials with vitamin B₁₂,

mecobalamin, folic acid, thiamine, acetyl-L-carnitine are still in progress (70, 73, 74, 75).

Nimodipine, a calcium channel blocker has been tested (76) and is known to affect primarily brain vasculature. It increases cerebral blood flow and reduces focal ischaemia (77). Memory related intraneuronal mechanisms are affected by calcium activated enzymes. Aging or dementia may result in dangerously high intraneuronal calcium levels. Calcium ions are especially toxic to hypoxic neurons. Hence, calcium channel blockers may be helpful by blocking calcium entry into injured or hypoxic neurons (78). Flunarizine hydrochloride which has more activity at the cellular level and less vascular effect may also be useful in patients with early dementia of Alzheimer's type (79). Immune mediated autodestructive processes may occur in Alzheimer's disease and hence exploration of the effectiveness of anti-inflammatory agents may be warranted (80). Potassium-channel blockers such as 4-aminopyridine, DGAVP Citrate (Org 5667) a vasopressin related peptide and D-cycloserine have been considered for treatment of Alzheimer's disease but the results are inconclusive (81, 82, 83).

Of the various categories of drugs used to improve cognitive functions, anticholinesterases, nootropics and calcium channel blockers seem to hold the most promise. Alzheimer's disease is a progressive degenerative dementia and no medication so far is predicted to reverse its course. Because Alzheimer's disease involves multiple defects, multi-drug treatment regimens may offer the best chance for effective therapy (84). In conclusion, we can hope to achieve beneficial therapy for Alzheimer's disease and senile dementia within this decade by using drugs which have specific effects on cognitive functions.

DRUGS PRODUCING COGNITIVE DYSFUNCTION

In the past 15 years, a number of clinical studies have evaluated the effect of antiepileptic drugs on cognitive performance (85). Because of its sedative properties, phenobarbital has long been cited for its potential cognitive effects. In an epidemiological survey of drug reactions with antiepileptic therapy, we have observed spontaneous reporting by patients about

cognitive difficulties such as forgetfulness, loss of memory, loss of concentration (86). The highest incidence (4-6%) of such reactions is reported by patients receiving phenobarbitone. Phenytoin sodium also produce similar effects, but incidence is lower. Camfield and Camfield (87) studied the nature of phenobarbital induced effects on cognition in otherwise, healthy children presenting with febrile seizures. Memory and concentration scores decreased as drug levels increased in phenobarbital treated patients. From their study, these authors concluded that phenobarbital has potential for long term cognitive and behavioural effects. Phenytoin, carbamazepine, sodium valproate and clobazam have been studied for cognitive effects. Phenytoin affects performance on neuropsychological tests of problem solving and visuomotor tasks. Ability to pay attention is also impaired. Impairment especially in motor or timed activities is greater when blood levels are in the upper levels of the therapeutic range.

Carbamazepine may have some adverse effects on task performance although impairment is less with carbamazepine than with phenytoin or phenobarbital. Valproate has shown no effect on learning tasks when added to preexisting therapy and produced minimal adverse effects on psychological tests. Selection of the drug, monotherapy, optimal dosage and withdrawal at the right time are factors which can have an impact on cognitive dysfunction.

Psychopharmacological agents such as benzodiazepines, lithium, tricyclic antidepressants are known to influence learning and memory. Recently a growing number of anecdotal reports have indicated that triazolam, a short acting benzodiazepine tend to cause anterograde amnesia (88). Some detrimental effects on selective attentional functioning have been observed after triazolam. Another category of drugs which may impair memory are steroids (89).

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