ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Drug Induced Cognitive Impairment

TK Karthik Raja [1], N Venkateswaramurthy [1*], R Sambath Kumar [2]
Department of Pharmacy Practice[1],
Department of Pharmaceutics [2],
J.K.K.Nattraja College of Pharmacy, Kumarapalayam-638183, Tamil Nadu, India.
venkateswaramurthy.n@jkkn.ac.in

Abstract:
As a result of taking drugs, elderly patients are more likely than younger patients to acquire cognitive impairment. Drug-induced cognitive impairment is a major cause of delirium and a common complicating factor in dementia diagnosis. Age, brain disease, and addiction to alcohol and/or drugs are all risk factors for delirium.The elderly are highly susceptible due to impaired renal and liver functions associated with multiple diseases, multiple drug use, and age-related pharmacokinetic and pharmacodynamic changes. Drugs have a negative effect on cognitive functions due to the following pathophysiological mechanisms: a decrease in neuronal excitability, an increase in gamma-aminobutyric acid activity, and decreases in enzyme activity, the number of receptors, cerebral perfusion, and brain atrophy; additionally, a number of mechanisms have not been thoroughly studied. Dementia and delirium can be caused by psychoactive drugs, antidepressants, and anticonvulsants. Nonpsychoactive pharmaceuticals including histamine H2 receptor antagonists and cardiac treatments can also produce acute or persistent cognitive problems. The risk of drug-induced impairment can be reduced by implementing strategies that improve overall health, avoiding unnecessary medications, and selecting medications that are less likely to cause delirium.

Keywords: Cognitive impairment, Dementia, Delirium, Elderly patients

1. INTRODUCTION:

When a person has problems inrecalling, acquiring new knowledge, concentrating, or making judgments that influence their everyday lives, they are said to have cognitive impairment.Cognitive impairment can range from mild to severe, with mild impairment referring to when people perceive changes in cognitive functioning but are still able to go about their daily lives. The ability to understand the meaning or importance of things, as well as the ability to talk and write, is lost in severe impairment, resulting in the inability to live independently. [1]

According to estimations, the population of those over 60 years old in India will have risen from 7.7% in 2001 to 12.30% by 2025, with nearly 150 million aged people in the country. [2] Dementia, commonly known as cognitive impairment, is a rather prevalent illness among the elderly. The majority of people with cognitive disabilities live in countries with a low and moderate income (60 percent in 2001, expected to rise to 71 percent by 2040); India's rate of increase in cognitive disability over the decades is expected that the figure will be around 300 percent, compared to only 100 percent in high-income countries.[3] In the majority of cases, a neurologically degenerative condition is the root reason for significant cognitive decline.[4]

Between normal ageing and dementia, there is a stage in the ageing process known as cognitive impairment.It describes a clinical scenario in which a person has memory complaints and objective evidence of cognitive impairment but no indication of dementia.[5]Although cognitive impairment is frequent in later age and may be related to the natural process of ageing, Alzheimer's disease (AD) neuropathological changes begin in the brain in the fifth decade of life, years before clinical symptoms appear.[6]

After the age of 60, the prevalence of dementia doubles every 5 years.[7]In the year 2000, India had 3.5 million Alzheimer's disease/dementia patients, compared to 4.5 million in the United States (USA).[8]The most common type of dementia is Alzheimer's disease, which is defined as an acquired cognitive and behavioural impairment severe enough to significantly restrict social and occupational functioning. [9]

One of the most frequent reversible and preventable consequences linked with acute and chronic alterations in cognition is drug-induced cognitive impairment. In vulnerable patients, most drugs can cause some level of cognitive impairment or problems; however, particular medication types are more frequently implicated.[10] Drug-induced cognitive impairment is more common in some groups. Confusion, delirium, and dementia are all substantial risk factors for advanced age, cognitive impairment, and dementia.[11]The aetiology of drug-induced cognitive impairment is frequently complex. Age and sickness are known to cause changes in pharmacokinetics, pharmacodynamics, brain homeostasis, blood-brain barrier permeability, and neurochemistry. [12,13] Additionally, an increased number of comorbidities, frailty, concomitant cognitive impairment, high pill burden, and supratherapeutic pharmaceutical serum concentrations, such as digoxin, have all been identified as key factors in predisposing an individual to drug-induced cognitive impairment. [14]Because drug-induced cognitive impairment is frequently reversible, it is critical to perform a full medication reconciliation to ensure that the offending substance is identified and removed as soon as possible (s). Furthermore, preventative efforts such as avoiding high-risk drugs wherever possible, particularly in the most vulnerable, and/or appropriately adjusting doses based on age or pathophysiology-related changes, as well as regular follow-up and monitoring, may help to avoid issues.[15]According to AARP findings there are ten class of drugs that cause cognitive impairment and they are Antianxiety drugs, Cholesterol drugs, Antiseizure drugs, Antidepressant drugs, Narcotic painkillers, Parkinson's

drugs, Hypertension drugs, Sleeping aids, Incontinence drugs, Antihistamines

2. STATINS INDUCED COGNITIVE IMPAIRMENT:

Statins are inhibitors of the 3-hydroxy-3methylglutaryl coenzyme (HMG-CoA). A reductase is a type of enzyme that has been used to treat hypercholesterolemia and ASCVD (atherosclerotic cardiovascular disease).[16]In most developed nations, ASCVD is one of the leading causes of illness and mortality, and its prevalence is steadily rising.Statins diminish the amount of 24Shydroxycholesterol, a main product of brain cholesterol metabolism, in patients with Alzheimer's disease, in addition to their lipid-lowering actions in the plasma.Studies on the effects of statins on the central nervous system include case studies, observational studies, and randomised clinical trials, with metaanalyses revealing inconsistent results. Statins are the most effective medications for lowering plasma cholesterol, and they are also well tolerated.[17]Statins can also decrease tumour cell proliferation while increasing intracellular calcium mobilisation. In rodents, HMG CoA reductase has been demonstrated toreduce the production of osteoclasts, while human individuals treated with statins have showed a decrease in the number of bone fractures.[16]

Despite the fact that a reevaluation of statin clinical trial data found no effect on cognition, case reports and research continue to suggest that statins can cause cognitive impairment in some patients.Likewise, the FDA addressed the issue of cognitive impairment in a 2012 notice, stating that statins may cause reversible cognitive impairment. To properly evaluate the level of knowledge on the effect of statins on cognition, careful study of the present evidence is required.[18] By 2020, there will be almost 700 million people aged 60 and up living in emerging countries.However, in most nations, there are few studies that look at the distribution of risk factors for cognitive impairment.[19] The purpose of this article is to examine the present evidence on statins' claims that they cause cognitive impairment. Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, and Simvastatin, according to AARP, are statin medicines that induce cognitive impairment.

Researchers looked at the AERS database for the effects and to see if the evidence could be used to identify patients at higher risk, according to the FDA announcement. There have been 2597 claims of cognitive impairment, with a substantially higher incidence of adverse reports of cognitive dysfunction connected to potent lipophilic statins like Atorvastatin and Simvastatin. They claimed that lipophilic statins including atorvastatin, simvastatin, lovastatin were identified as the most usually connected with the cognitive impairment. When atorvastatin and simvastatin are used instead of other statins, there are more complaints of side effects.[20]

However, as compared to other stains, atorvastatin and simvastatin had a higher prevalence of cognitive impairment reports, implying that lipophilicity is to blame for the increased incidence of cognitive impairment. The fact that lipophilic statins like atorvastatin and simvastatin have a higher blood-brain barrier crossing than hydrophilic statins like pravastatin and rosuvastatin led to the theory that statins can induce cognitive impairment. [21]

2.1 Statins induced cognitive impairment possible mechanism :

Two possible mechanism has been proposed: (1) Statins diminish the availability of cholesterol, which may compromise the integrity of neuronal and glial cell membranes, which is resulting in the slowed conduction of the neuronal impulses.[22]

(2) The reduced re-myelination and also reduction in the coenzyme Q10 levels would impair the mitochondrial function and it may lead to the increase in the oxidative stress.[23]

2.2 Statin's and reversible cognitive impairment :

However in a study examining, the long-term effects of pravastatin and atorvastatin treatment in adult rats, researchers discovered that pravastatin impairs learning, implying an impact on working memory and object recognition memory that was reversible when the drug was stopped, whereas atorvastatin had no effect on either task.Because pravastatin is hydrophilic while atorvastatin is lipophilic, this model contradicts the theorised mechanism of lipophilic statins producing more cognitive damage. [24]Researchers in Australia conducted a review of two randomised control trials on simvastatin and pravastatin that covered a large number of patients but found no link between statin use and cognitive decline. However, there have been case reports of statins causing memory loss that have been published.[25]

In a review 60 case reports has been described the main symptom of short term memory loss that has been occurred a few months after the start of the statin therapy and also several case reports has been observed the resolution of the cognitive impairment upon the discontinuation of the statins and the recurrence of the cognitive impairment upon rechallenging of the statins.[26]

Patient survey based analysis also found that the evidence of cognitive impairment with the variable onset and the recovery courses this will provide a clear relation of statin potency and negative impact on the quality of life.[27]

Naranjo ADR probability scale also been used to describe the relationship between the statins and the cognitive impairment. This would be the widely accepted tool to measure the relation between the adverse event and the medication. On this basis, it was determined that 75% of the cognitive impairments were probably or definitely connected to statin therapy. [28]

In a study of 60 patients with memory loss associated with statins, 50 percent of the patients showed cognitive adverse effects within two months of treatment, with 36 patients receiving simvastatin, 23 receiving atorvastatin, and one receiving pravastatin. The United States Food and Drug Administration (FDA) amended the statin labelling in 2012, warning of the risk of cognitive impairment and later adding to the concerns about cognitive decline. [29]

3. ANTICHOLINERGIC INDUCED COGNITIVE IMPAIRMENT:

Anticholinergics are commonly used in the elderly to treat overactive bladder and Parkinson's symptoms. Anticholinergic characteristics are found in several medications often recommended to the elderly, including antiemetics, antispasmodics, bronchodilators, anti-arrhythmic agents, and antihistamines. These medicines have long been suspected of causing cognitive loss and exacerbating dementia symptoms. [30]

Scopolamine and atropine are typically associated with cognitive abnormalities, such as hallucinations and overt delirium, even at extremely low doses. These drugs are antiemetics and antisecretory substances that have traditionally been used as premedications prior to surgery. However, surgical delirium and delayed or disrupted awakening from anaesthesia were prevalent issues.[31]The use of glycopyrronium, a peripherally acting anticholinergic, rather than atropine has been demonstrated to minimise the risk of postoperative delirium. [32]

Anticholinergic mydriatics can have systemic side effects, including disorientation in the elderly. Low-concentration atropine eyedrops, for example, have been linked to delirium following cataract surgery.[33] In individuals with urinary incontinence or frequency, oxybutinin is used to control unrestrained bladder contractions. It has recently been discovered that oxybutinin can produce cognitive problems in the elderly, as well as delirium.[34]

3.1 Anticholinergic induced Possible mechanism :

Anticholinergic medications block the neurotransmitter acetylcholine from binding to muscarinic receptors in the brain, thereby suppressing it.Furthermore, there is mounting evidence that anticholinergics have a stronger impact on older people due to their capacity to cross the blood–brain barrier.[35]The cumulative effect of one or more anticholinergic medicines on an individual, which is exacerbated by age-related pharmacokinetic and pharmacodynamic changes, is known as anticholinergic load.Specific drugs with strong anticholinergic activity or a combination of pharmaceuticals with low, medium, and high anticholinergic burden can result in a higher anticholinergic burden. Inhibition of acetylcholine transmission to the central nervous system is caused by an increase in circulating anticholinergic activity, implying a cholinergic deficit that is thought to be implicated in producing poor cognitive and motor function.[36]

Surprisingly, a large-scale cohort study of elderly people found moderate cognitive impairment (MCI) in 80 percent of patients taking anticholinergic medications, and concluded that this therapy increases the risk of MCI by fivefold.[37] According to a 6-year observational research in an African-American population, 53% used a potential anticholinergic and 11% used a definite anticholinergic; the usage of definite anticholinergics was linked to an elevated risk of cognitive impairment.[38]Similarly, a four-year follow-up study in France found that 7.5 percent of participants were taking anticholinergics, and that their use was linked to an increased risk of cognitive decline and dementia, which remained significant even after accounting for multiple possible codeterminants of cognitive decline.[39]In a German observational trial, 37 percent of the patients used anticholinergics, and they had a higher risk of dementia (hazard ratio=2.081) as a result of anticholinergic activity. [40]

4. CARDIOVASCULAR AGENTS INDUCED COGNITIVE IMPAIRMENT:

Antiarrhythmics (eg, disopyramide, quinidine), cardiac glycosides (eg, digoxin), and sympathetic antihypertensives (eg, clonidine, methyldopa, propranolol, reserpine) have all been linked to cognitive impairment. Impairment might range from simple delirium and confusion to more long-term cognitive problems. 1-6 Cardiovascular drugs can impair cognition through a variety of routes. [41]

Low-cerebral perfusion situations linked with hypotension, bradycardia, and progressive or full heart block due to atrioventricular node inhibition can lead to impaired cognitive performance, notably in the domains of direction, attention, and memory. [42] Although it is an important issue to consider, arterial hypertension raises the cerebrovascular disease riskand is one of the key risk factors for the development of vascular dementia. Hypertension has also been related to an increased risk of Alzheimer's disease caused by unknown causes.[43]

When administered as part of a multitherapy regimen or in the face of severe nausea/vomiting or renal impairment, diuretics can cause dehydration as well as electrolyte and/or acidbase imbalances.[44]This can cause confusion and put you at risk of delirium. Additionally, despite serum digoxin concentrations within the approved therapeutic concentration (2.0 ng/mL), hypokalemia and hypomagnesemia caused by the use of thiazide and loop diuretics24 may enhance digoxin toxicity, such as disorientation and delirium. [45]

Antihypertensives with sympathetic nervous system inhibiting capabilities, such as beta blockers, have been associated to cognitive abnormalities in a number of studies. Deficits in cognitive function, including memory, have been reported in reports. [46]

In the cortical and subcortical regions, reserpine, methyldopa, and clonidine can affect the release of different catecholamines and/or serotonin (5-HT). This can lead to neuropsychiatric issues including confusion, delirium, and depression, as well as cognitive issues like memory lapses and poor focus.[47]When pharmaceuticals are used in high or toxic doses, the risk of side effects increases; as a result, careful medication dosing adjustments for each patient should be made.Reserpine depletes 5-HT, dopamine, and norepinephrine reserves in the central nervous system. Following reserpine withdrawal, both cardiovascular and CNS effects may linger for some time. New vesicles can be synthesised to restore sympathetic activity, although this takes many weeks. Methyldopa is transformed to alpha-methyl-noradrenaline, a bogus neurotransmitter that depletes norepinephrine levels.[48]Clonidine acts as an agonist at presynaptic alpha2-receptors in the brain, inhibiting

norepinephrine release into neuronal synapse and causing CNS depression through increased inhibitory neurotransmission. 24 It is roughly 50% converted in the liver to inactive metabolites, whilst approximately 50% of the parent drug is eliminated unaltered in urine. Supratherapeutic/toxic serum concentrations are linked to an increased risk of CNS depression, miosis with considerable hypotension, and bradycardia due to clonidine overdose, compounding mistake, intrathecal pump malfunction, and a significant decrease in metabolism and elimination.[49]

Digoxin is a medication with a restricted therapeutic index that inhibits the enzyme sodium/potassium (Na/K) ATPase. Digoxin's neurotoxic impact has been linked to a number of neuropsychiatric side effects, including visual disturbances, anxiety, sadness, confusion, hallucinations, and delirium.[50]As a result of the accumulation, the risk of digitalis cardiotoxicity and neurotoxicity increases. Because digoxin is mostly removed in its unmodified form by glomerular filtration, it has a propensity to accumulate in older adults or those with poor renal function.[45]The Pglycoprotein transport system in the gastrointestinal tract and kidneys is also a substrate for digoxin. Increased oral absorption of digoxin (increased bioavailability) and/or lower renal clearance result from inhibiting this cellular drug efflux pump. Interactions with drugs that are powerful inhibitors of the P-glycoprotein transport system, such as verapamil, amiodarone, and quinidine, cause digoxin concentrations to rise considerably.[51]When oral digoxin is combined with amiodarone, the serum concentration of digoxin rises by 70%. [52] When quinidine is used with either oral or intravenous digoxin, the digoxin serum concentrations rise by 100 percent or 54 percent to 83 percent, respectively. Increased digoxin serum concentrations above the therapeutic limit are thought to be linked to a significant disruption of neuronal activity due to a change in the physiologic function of the Na/K ATPase. This raises intracellular calcium levels and pushes magnesium out of its binding sites. As a result of this disruption, mitochondrial ATP synthesis is reduced, and Na/K ATPase is further inhibited. [53]

5. ANTIPSYCHOTICS INDUCED COGNITIVE IMPAIRMENT:

According to a major retrospective study, 1% of phenothiazines patients in a psychiatric hospital had delirium.[54]Patients who took many drugs were at higher risk, as were those who were older. Neuroleptic medicines were also found to be an independent risk factor for delirium in general hospital patients, according to Schor et al. However, it may be argued that in this study, neuroleptic drug prescriptions were a reaction to rather than a cause of delirium.[55] Several antipsychotics have been shown to have significant anticholinergic activity, which may help to explain why they might cause or aggravate delirium. Clozapine, a novel atypical neuroleptic with the same affinity for muscarinic receptors as amitriptyline, thioridazine, which has roughly one-sixth the anti-muscarinic activity of amitriptyline, and chlorpromazine are among them.[56] In elderly patients, newer antipsychotics such as risperidone, which has a high affinity for serotonin and dopamine receptors but no anticholinergic effect, are being employed. Risperidone has been linked to delirium, which is unusual. [57]

When a patient on neuroleptics develops delirium, the neuroleptic malignant syndrome (NMS) should be addressed. Muscle rigidity, autonomic instability, and fluctuating consciousness are all symptoms of this potentially lethal condition.[58] Dehydration, long-acting or high-dosage neuroleptics, fast dose increases with neuroleptics, sudden withdrawal of antiparkinsonism drugs or neuroleptics, and concurrent lithium therapy are all predisposing factors.Withdrawal of neuroleptic medicines, supportive measures, and the administration of dantrolene or bromocriptine are all part of the treatment. NMS has been recorded in the elderly, despite being mostly an illness of younger individuals. [59]

Based on data from a prospective analysis of 104 dementia patients, McShane et al have found a probable relationship between antipsychotic medication prescription and faster cognitive deterioration.[60]Twenty patients who were prescribed antipsychotic drugs had double the rate of cognitive impairment as those who were not. Antipsychotic medicines having high anticholinergic activity, which have been associated to the development of chronic as well as acute cognitive impairment in many patients, could be one explanation for this observation. [61]

6. HYPNOTICS/SEDATIVES INDUCED COGNITIVE IMPAIRMENT:

Benzodiazepines have been associated to delirium and dementia. In a prospective analysis of 229 senior hospital patients, benzodiazepine toxicity was found in 7 of 50 individuals with delirium. In a case-control study, benzodiazepines were used to treat 21% of 91 patients with postoperative delirium and 8% of 154 controls. Delirium was linked to longer-acting benzodiazepines such flurazepam and diazepam, as well as high dose therapy (greater than diazepam 5mg/day or similar).The most prevalent medicines that cause dementia are long-acting benzodiazepines.[51]Dementia was connected to ongoing medication with a single benzodiazepine in 13 participants in a sample of 308 patients with probable dementia.Similar findings have been reported by others.[62]Barbiturates, which are currently less often used, can produce chronic cognitive impairment that can be mistaken for Alzheimer's disease.Sedative toxicity, in general, causes excessive sedation, decreases the risk of delirium or dementia, albeit actual delirium or dementia caused simply by these medicines is unlikely.

Surprisingly, growing awareness of sedative medicines' negative long-term cognitive (and other) effects has led to an increase in the probability of withdrawal symptoms. In hospital patients, abrupt withdrawal from short-acting benzodiazepines is a common cause of delirium. Withdrawal symptoms from long-term barbiturate therapy are significantly more severe. Delirium owing to rapid cessation of sedative medicines is hyperactive, with florid hallucinations and considerable autonomic overactivity, similar to delirium tremens caused by alcohol withdrawal.[63]

7. ANTIEPILEPTICS INDUCED COGNITIVE IMPAIRMENT:

All anticonvulsant medications have the potential to impair cognitive function. Delirium and dementia are among the symptoms that have been described. The traditional belief is that phenytoin, primidone, and phenobarbital induce the most severe cognitive deficits, whereas sodium valproate, carbamazepine, and the newer anticonvulsants cause only minor problems.[64]However, determining the cognitive effects of anticonvulsants independent of other factors is difficult due to the high prevalence of underlying brain disease, particularly in elderly people with seizures, the occurrence of psychiatric problems such as delirium and psychosis during and after seizures, and the proclivity of anticonvulsants to be involved in drug interactions. [65]

Delirium, on the other hand, is a rare side effect of sodium valproate and may be caused by an ammonia buildup. The use of phenytoin has been associated to the development of delirium and dementia.[66] Patients with polypharmacy had the most cognitive impairment from anticonvulsant medicines, and rationalising their treatment improves their cognitive capacities. Because of changes in pharmacokinetics, the concept of a therapeutic drug level is less applicable in older people, and CNS toxicity can occur within the 'typical' therapeutic range of anticonvulsant drugs. [64]

Gabapentin has a novel mode of action that involves GABA-mediated inhibition potentiation and maybe sodium channel inactivation. GBP has few negative cognitive implications and has few central nervous system (CNS) adverse effects, even at high doses or with rapid dosage escalation.[67]Topiramate is a broad-spectrum AED with several modes of action, including voltage-dependent sodium channel blockage, potentiation of GABA-mediated effects, inhibition of carbonic anhydrase, and glutamate antagonism. TPM is the newer AED that is causing the most worry because of its possible deleterious neuropsychological consequences, which include impaired language and frontal execution function. In clinical trials, topiramate has been shown to cause somnolence, mental slowness, memory loss, and linguistic issues.[68]TPM is a broad-spectrum AED with several modes of action, including voltage-dependent sodium channel blocking, GABA potentiation, carbonicanhydrase inhibition, and glutamate antagonism. TPM is the newer AED that is causing the most worry because of its possible deleterious neuropsychological consequences, which include impaired language and frontal execution function. TPM has been proven in clinical trials to cause somnolence, mental sluggishness, memory loss, and language problems.[69]

Vigabatrin (VGB) is a structural analogue of GABA that elevates brain GABA levels by irreversibly inhibiting the degradative enzyme GABA-transaminase. Because of indications of visual field constriction as a side effect, its usage in epilepsy treatment is limited. In a double-blind, randomised add-on study, VGB had few negative effects on cognitive or quality-of-life parameters in epilepsy patients when compared to placebo. [70]

Zonisamide (ZNS) operates by inhibiting carbonic anhydrase and blocking presynaptic voltage-sensitive sodium and calcium channels in neurons. It also increases cortical GABA concentrations. When ZNS was taken for 12 to 24 weeks in two exploratory investigations, it appeared to affect cognitive processes such as attention, memory, and language function. The poorer cognitive function observed after 12 weeks of treatment tended to improve after 24 weeks.[71]However, even after 6 months of medication, a considerable proportion of epilepsy patients who used ZNS as a monotherapy complained of memory loss (35%) and attention deficit (27%), suggesting that long-term ZNS treatment causes severe cognitive impairment. In a prospective, randomised, open-label study, the long-term cognitive effects of ZNS monotherapy in epilepsy patients were recently clarified.Despite the fact that ZNS medication reduced seizure frequency and EEG abnormalities after a year, several cognitive tests revealed poor results. The poor performance could have been due to the dosage, particularly those over 300 mg per day. In conclusion, the limited research that have been done demonstrate that ZNS has negative impacts on cognition.[72]

8. ANTIDEPRESSANT DRUGS INDUCED COGNITIVE IMPAIRMENT:

Tricyclic antidepressants (TCA) with considerable anticholinergic effects are the most common cause of antidepressant drug-induced confusion. In an assessment of adverse drug reactions among more than 15,000 mental inpatients, TCA-induced delirium was reported to be 1.2 percent. A analysis of published data on 976 TCA-treated people found that 58 (6%) of them suffered CNS impairment. [73]TCA levels in the blood, advanced age, and female gender, in that order, were all risk factors for delirium.Amitriptyline, an antidepressant with the highest affinity for human brain muscarinic receptors, has been linked to delirium the most. About 5% of elderly individuals using amitriptyline or imipramine became delirious, according to studies. Tricyclic antidepressants like desipramine and nortriptyline, which have less anticholinergic effect, are better for the elderly.[74]

Other antidepressants, such as selective serotonin reuptake inhibitors (SSRI) and monoamine oxidase inhibitors (MAOI), are less likely to produce delirium or significant cognitive impairment. When an SSRI is coupled with a MOAI, clomipramine, or selegiline, the'serotonin syndrome' — a state of delirium, autonomic instability, and rigidity – might ensue.[75] Hyponatraemia caused by SSRIs can sometimes cause delirium. Delirium is another well-known symptom of lithium poisoning.[76]

9. ANTIHISTAMINES INDUCED COGNITIVE IMPAIRMENT:

Acute CNS damage, including delirium, has been linked to all histamine-2 (H2) receptor blockers. Despite the fact that cimetidine has been implicated in the majority of cases, a review of the literature found no indication of variations in the incidence of CNS responses to other H2 blockers. While some patients may tolerate a different H2 blocker, others may have delirium again. Also, delirium has been documented as a side effect of omeprazole and other proton pump inhibitors.[77]

While CNS toxicity from H2 blockers is uncommon in outpatients, it has been observed in 1-2 percent of all hospital patients and 15-80 percent of critical care patients. The majority of toxicity occurs in the elderly.[78]Some research suggests that people with renal failure are more likely to experience these problems. In a prospective open analysis of 41 individuals treated with intravenous ranitidine, confusion occurred in 6/20 patients with an estimated creatinine clearance less than 50mL/min and 0/20 patients with a clearance more than 50mL/min.[79]Patients with greater average peak and trough ranitidine levels were more likely to develop it.In certain patients with cimetidine-induced disorientation, a link has been discovered between CNS symptoms, drug dose, and plasma or cerebrospinal fluid levels. However, CNS damage from H2 blocker overdose is uncommon, and several cases of H2 blocker-induced delirium have been reported with normal organ function and standard drug doses. [78]

At this time, the consequences of H2 blockage on the central nervous system remain unknown. Anticholinergic effects of histamine blockers have been seen, and the remission of H2 blocker delirium after treatment with physostigmine suggests that this mechanism is involved.[80]

10. CONCLUSION:

When a person has difficulty remembering things, learning new things, concentrating, or making decisions, this is referred to as cognitive impairment, and it has an impact on day-to-day life. Memory difficulties and some medicines, such as benzodiazepines and anticonvulsants, anticholinergics, statins, and others, were linked in our study.According to statin report compared to other stains, atorvastatin and simvastatin had a higher prevalence of cognitive impairment reports, implying that lipophilicity is to blame for the increased incidence of cognitive impairment. According to Anticholinergic drugs it may have the systemic side effects, including disorientation in the elderly patients according to recent study Oxybutynin will cause cognitive impairment. Although study suggest that elderly patients are more prone to cognitive impairment. The treatment of patients with cognitive impairment necessitates a thorough examination of all drugs that may be contributing to or causing the impairment, individually or in combination.This is rarely simple, and it's even more challenging in critically ill hospital patients with delirium. It is sometimes difficult to be certain that medicines are the cause of delirium in these individuals, and even more difficult to pinpoint a specific substance as the precipitant.Patients are likely to benefit from the discontinuation of medications with unknown indications if their cognitive status does not change. Anticholinergic and antipsychotic medicines are the most common suspects for producing drug-induced cognitive impairment. However, in delirious individuals, it's often best to discontinue as many medications as possible right once, even if this makes it more difficult to figure out which drug was the source of the problem later.

Conflicts of Interest: Authors declare that they have no conflicts of interest.

Funding statement: This review did not receive any funding.

REFERENCE:

1. Herbert, L.E., Scherr, P.A., Bienias, J.L., *et al.,* Alzheimer's disease in the U.S. population: Prevalence estimates using the 2000 census. *Archives of Neurology*. 2003, 60, 1119–1122.
2. Bose, A., Shankardass, M.K., Growing old in India: voices reveal, statistics speak. New Delhi: BR Publishing Corporation. 2000, 244–246.
3. Ferri, C.P., Prince, M., Brayne, C., *et al.,* Global prevalence of dementia: a Delphi consensus study. *Lancet.* 2005, 366, 2112–2117.
4. Ritchie, K., Lovestone, S., The dementias. *Lancet*. 2002, 360, 1759–1766.
5. Burns, A., Zaudig, M., Mild cognitive impairment in older people. *Lancet*. 2002, 360, 1963-1965.
6. DeCarli, C., Mild cognitive impairment: Prevalence, prognosis, aetiology, and treatment. *Lancet Neurol*. 2003, 2, 15-21.
7. Upadhyay, P., Panjwani, D., Yadav, A.K., Neuropathology staging and treatment strategies of Alzheimer's disease: an update. *Int J Nutr Pharmacol Neurol Dis*. 2014, 4, 28– 42.
8. Plassman, B.L., Langa, K.M., Fisher, G.G., *et al.,* Prevalence of dementia in the United States: the ageing demographics and memory study. *Neuroepidemiology*. 2007, 29,125–132.
9. Albert, M.S., Dekosky, S.T., Dicksond, D., Duboise, B., *et al.,* The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011, 7, 270–279.
10. Clegg, A., Young, J.B., Which medications to avoid in people at risk of delirium: a systematic review. *Age Ageing*. 2011, 40(1), 23-29.
11. Ancelin, M.L., Artero, S., Portet, F., *et al.,* Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ.* 2006, 332(7539), 455- 459.
12. Corsonello, A., Incalzi, R.A., Pedone, C., Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. *Curr Med Chem*. 2010, 17(6), 571-584.
13. Trifiro, G., Spina, E., Age-related changes in pharmacodynamics: focus on drugs acting on central nervous and cardiovascular systems. *Curr Drug Metab*. 2011, 12(7), 611-620.
14. Wolff, J.L., Starfield, B., Anderson, G., Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med*. 2002, 162(20), 2269-2276.
15. Eichhorn, E.J., Gheorghiade, M., Digoxin. *ProgCardiovasc Dis*. 2002, 44(4), 251-266.
16. Vaughan, C.J., Gotto, A.M., Basson, C.T., The evolving role of statins in the management of atherosclerosis. *J. Am. Coll. Cardiol*.2000, 3, 1-10.
17. Bellosta, S., Ferri, N., Bernini, F., *et al.,* Non-lipid-related effects of statins. *Ann. Med.*2000, 32, 164-176.
18. Blum, C.B., Comparison of properties of four inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. *Am. J. Cardiol*. 1994, 73, 3-11.
19. Blumenthal, R.S., Statins: Effective antiatherosclerotic therapy. *Am. Heart. J*.2000, 139, 577- 583.
20. Sahebzamani, F.M., Munro, C.L., Marroquin, O.C., *et al.,* Examination of the FDA Warning for Statins and Cognitive Dysfunction. *Aust J Pharm*. 2014, 2, 141.
21. Deborah, S., Amanda, J., Cognitive Impairment Associated with Atorvastatin and Simvastatin. *Pharmacotherapy*.2004, 23(12), 1663-7.
22. Miron, V.E., Zehntner, S.P., Kuhlmann, T., *et al.,* Statin therapy inhibits remyelination in the central nervous system. *Am J Pathol*. 2009, 174(5), 1880–1890.
23. Langsjoen, P.H., Langsjoen, A.M., The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10. A review of animal and human publications. *Biofactors*. 2003, 18(1-4), 101–111.
24. Stuart, S.A., Robertson, J.D., Marrion, N.V., Chronic pravastatin but not atorvastatin treatment impairs cognitive function in two

rodent models of learning and memory. *PLoS One*. 2013, 8(9), e75467.
25. Jamolowicz, A.I., Chen, H.Y., Panegyres, P.K., Statins and memory loss: an Australian experience. *Australas Med J*. 2015, 8(3), 73–79.
26. Muldoon, M.F., Ryan, C.M., Sereika, S.M., *et al.*, Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *Am J Med.* 2004, 117(11), 823–829.
27. FDA. FDA drug safety communication: important safety label changes to cholesterol-lowering statin drugs. Available from: http://www.fda.gov/ Drugs/DrugSafety/ucm293101.htm.
28. Parker, B.A., Polk, D.M., Rabdiya, V., *et al*., Changes in memory function and neuronal activation associated with atorvastatin therapy. *Pharmacotherapy.* 2010, 30(6), 625.
29. Wagstaff, L.R., Mitton, M.W., Arvik, B.M., Statin-Associated Memory Loss: Analysis of 60 Case Reports and Review of the Literature. *Pharmacotherapy*. 2003, 23, 871–880.
30. Cummings, J.L., Behavioural complications of drug treatment in Parkinsons disease. *J Am GerSoc.* 1991, 39,708-716.
31. Molchan, S.E., Martinez, R.A., Hill, J.L., *et al.*, Increased cognitive sensitivity to scopolamine with age and a perspective on the scopolamine model. *Brain Res.* 1992, 17, 215-226.
32. Sheref, S.E., Pattern of CNS recovery following reversal of neuromuscular blockade. Comparison of atropine and glycopyrollate. *Br J Anaesthesia.* 1985, 57, 188-191.
33. Summers, W.K., Reich, T.C., Delirium after cataract surgery: review and two cases. *Am J Psychiatry*. 1979, 136, 386-391.
34. Donnellan, C.A., Fook, L., McDonald, P., Oxybutinin and cognitive dysfunction. *BMJ*. 1997, 315, 1363-1364.
35. Clare, V., Roy, L., Arduino, M., Association between prescribing of antimuscarinic drugs and antimuscarinic adverse effects in older people. *Expert Rev Clin Pharmacol*.2010, 3(4), 441-452
36. Schliebs, R., Thomas, A., The significance of the cholinergic system in the brain during aging and Alzheimer's disease. *J Neural Transm*. 2006, 113(11), 1625-1644.
37. Ancelin, M.L., Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study.*BMJ*. 2006, 332, 455-459.
38. Campbell, J.A., Postnatal hepatic fatty acid oxidative capacity of preterm pigs receiving TPN does not differ from that of term pigs and is not affected by supplemental arachidonic and docosahexaenoic acids. *J. Nutr*. 2010, 140, 752-759.
39. Carriere, I., Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. *Arch. Intern. Med*.2009, 169, 1317-1324.
40. Jessen, F., Anticholinergic drug use and risk for dementia: target for dementia prevention. *Eur. Arch. Psychiatry Clin. Neurosci*.2010, 260, 111-115.
41. Clegg, A., Young, J.B., Which medications to avoid in people at risk of delirium: a systematic review. *Age Ageing*. 2011, 40(1), 23-29.
42. Duschek, S., Schandry, R., Reduced brain perfusion and cognitive performance due to constitutional hypotension. *ClinAuton Res*. 2007, 17(2), 69-76.
43. Kivipelto, M., Ngandu, T., Fratiglioni, T., *et al.*, Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol*. 2015, 62(10), 1556-1560.
44. Yong, T.Y., Huang, J.E., Lau, S.Y., Severe hyponatremia and other electrolyte disturbances associated with indapamide. *Curr Drug Saf*. 2011, 6(3), 134-137.
45. Digoxin (digoxin tablet) package insert [Internet]. Silver Spring (MD): Food and Drug Administration [updated 2009 Aug; cited 2015 Sept 4]. Available from: http://www.accessdata.fda.gov/ drugsatfda_docs/label/2010/020405s004lbl.pdf.
46. Richardson, P.J., Wyke, M.A., Memory function–effects of different antihypertensive drugs. *Drugs*. 1988, 35(5), 80-85.
47. Webster, J., Koch, H.F., Aspects of tolerability of centrally acting antihypertensive drugs. *J CardiovascPharmacol*. 1996, 27(3), 49-54.
48. Sabayan, B., Oleksik, A.M., Maier, A.B., *et al.*, High blood pressure and resilience to physical and cognitive decline in the oldest old: the Leiden 85- plus Study. *J Am Geriatr Soc.* 2012, 60(11), 2014-2019.
49. Ruha, A.M., Levine, M., Central nervous system toxicity. *Emerg Med Clin North Am.* 2014, 32(1), 205-221.
50. Varriale, P., Mossavi, A., Rapid reversal of digitalis delirium using digoxin immune Fab therapy. *ClinCardiol*. 1995, 18(6), 351-352.
51. Kurup, R.K., Kurup, P.A., Hypothalamic digoxin, hemispheric chemical dominance, and sarcoidosis. *Int J Neurosci*. 2003, 113(11), 1593-1611.
52. Frewen, J., Savva, G.M., Boyle, G., *et al.*, Cognitive performance in orthostatic hypotension: findings from a nationally representative sample. *J Am Geriatr Soc*. 2014, 62(1), 117-122.
53. Haga, H., Effects of dietary magnesium supplementation on diurnal variation of blood pressure and plasma Naþ, K(þ)- ATPase activity in essential hypertension. *Jpn Heart J*. 1992, 33(6), 785-798.
54. Schmidt, L.G., Grohmann, R., Strauss, A., *et al.*, Epidemiology of toxic delirium due to psychotropic drugs in hospital. *Compr Psychiatry.* 1987, 28, 242-249.
55. Schor, J.D., Levkoff, S.E., Lipsitz, L.A., *et al.*, Risk factors for delirium in hospitalized elderly. *JAMA*. 1992, 267, 827-831.
56. Feinberg, M., The problems of anticholinergic adverse effects in older patients. *Drugs Aging*. 1993, 3, 335-348.
57. Ravena, R., Dolberg, O.T., Hirshmann, S., *et al.*, Delirium in elderly patients treated with risperidone: a report of three cases. *J Clin Psychopharmacology*. 1998, 18, 171-172.
58. Levenson, J.L., Neuroleptic malignant syndrome. *N Engl J Med*. 1985, 313, 163-166.
59. Finucane, P., Price, C., Ghose, K., Neuroleptic malignant syndrome in an elderly patient. *Br Med J*. 1988, 296, 14-18
60. McShane, R.N., Keene, J., Gedling, K., *et al.*, Do neuroleptics hasten cognitive decline in Dementia? *Br Med J*. 1997, 314, 266-270.
61. Larson, E.B., Kukull, W.A., Buchner, D., Adverse drug reactions associated with global cognitive impairment in elderly persons. *Ann Intern Med*. 1987, 107, 169-173.
62. Katz, I.R., Parmelee, P., Brubaker, K., Toxic and metabolic encephalopathies in long-term care patients. *Int Psycho geriatr*. 1991, 3, 337-347.
63. Francis, J., Martin, D., Kapoor, W.N., A prospective study of delirium in hospitalized elderly. *J Am Med Assoc*. 1990, 263, 1097-1101.
64. Trimble, M.R., Anticonvulsant drugs and cognitive function: a review of the literature. *Epilepsia*. 1987, 28 (3), 37-45.
65. Aldenkamp, A.P., Vermeulen, J., Phenytoin and carbamazepine: differential effects on cognitive function. *Seizure*. 1995, 4, 95-104.
66. Zaccara, C., Campostrini, R., Paganini, M., *et al.*, Long-term treatment with sodium valproate. *Ther Drug Monit*. 1987, 9, 34-40.
67. Chadwick, D.W., Anhut, H., Greiner, M.J., *et al.*, A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. International Gabapentin Monotherapy Study Group 945-77. *Neurology*. 1998, 51, 1282-1288.
68. Mula, M., Trimble, M.R., Thompson, P., Topiramate and wordfinding difficulties in patients with epilepsy. *Neurology*. 2003, 60, 1104-1107.
69. Lee, S., Sziklas, V., Andermann, F., *et al.*, The effects of adjunctive topiramate on cognitive function in patients with epilepsy. *Epilepsia.* 2003, 44, 339-347.
70. Dodrill, C.B., Arnett, J.L., Sommerville, K.W., Evaluation of the effects of vigabatrin on cognitive abilities and quality of life in epilepsy. *Neurology*. 1993, 43, 2501-2507.
71. Berent, S., Sackellares, J.C., Giordani, B., *et al.*, Zonisamide (CI-912) and cognition: results from preliminary study. *Epilepsia*. 1987, 28, 61.
72. Park, S.P., Hwang, Y.H., Lee, H.W., *et al.*, Longterm cognitive and mood effects of zonisamide monotherapy in epilepsy patients. *Epilepsy Behav*. 2008, 12, 102-108.
73. Preskorn, S.H., Jerkovich, G.S., Central nervous system toxicity of tricyclic antidepressants: phenomenology, course, risk factors, and role of therapeutic drug monitoring. *J Clin Psychopharmacol*. 1990, 2, 88-95
74. Branconnier, R.J., Cole, J.O., Effects of acute administration of trazadone and amitryptiline on cognition, cardiovascular function and salivation in the normal geriatric subject. *J Clin Psychopharmacology*. 1986, 1(6), 825-828.
75. Sporer, K.A., The serotonin syndrome. Implicated drugs, pathophysiology and management. *Drug Safety*. 1995, 13, 94-104.
76. Brown, A.S., Rosen, J., Lithium-induced delirium with therapeutic serum lithium levels: a case report. *J Geriatr Psychiatry Neurol*. 1992, 5, 53-55.

77. Picotte-Prillmayer, D., DiMaggio, J.R., Baile, W.F., H2 blocker delirium. *Psychosomatics*. 1995, 36, 74-77.
78. Cant, T.G., Korek, J.S., Central nervous system reactions to histamine-2 receptor blockers. *Ann Intern Med*. 1991, 114, 1027-1034.
79. Slugg, P.H., Haug, M.T., Pippenger, C.E., Ranitidine pharmacokinetics and adverse central nervous system reactions. *Arch Intern Med*. 1992, 152, 2325-2329.
80. Jenike, M.A., Levy, J.C., Physostigmine reversal of cimetidine-induced delirium and agitation. *J Clin Psychopharmacol*. 1983, 3, 43-44.