Review Article

Medicine that Causes Memory Loss: Risk of Neurocognitive Disorders

ABSTRACT

Medicine is one of the outstanding gifts of science to save lives. In addition to the desired therapeutic effect almost all of the medicine possesses the undesired secondary effect called side effect. From the over-the-counter (OTC) aspirin to the prescription medicine on the market, all drugs come with side effects. Numerous are negligible, few are problematic, some are major and certain are just weird. Almost any drug can cause nausea, vomiting or an upset stomach. Every medication carries some risks, although in some cases side effects are not noticeable as a result of sub-therapeutic concentration and memory loss are very common side effect of commonly used and prescribed drugs. The memory loss is one of the prominent causes of neurocognitive disorders, especially dementia, which is characterized by a disturbance of multiple brain functions, including memory, thinking, learning, reading calculation and judgement severe enough to reduce a person's ability to perform everyday activities. In addition to memory loss various factors as well as disorders contribute to the development of dementia. Alzheimer's disease (AD) is the most common form of neurodegenerative dementia. Including AD, Lewy body dementia and frontotemporal dementia give rise to progressive and irreversible loss of neurons and brain functions. At present, there are no treatments for these progressive neurodegenerative disorders. Medication associated with the risk of memory loss must be taken with more precaution. Therefore, the objective of this study is to show the risk of memory loss associated with antianxiety drugs (benzodiazepines), hypolipedemic drugs (statins), antiepileptic drugs (older and newer), antidepressant drugs (tricyclic antidepressants), narcotic painkillers (opioids), anti-Parkinson's drugs (dopamine agonists), antihypertension drugs (β-blockers), sleeping aids (nonbenzodiazepine sedative-hypnotics), incontinence drugs (anticholinergics and antimuscarinic) and antihistamines (first-generation).

Keywords: Memory loss; neurocognitive disorders; neurodegenerative dementia; Alzheimer's disease.

1. Introduction

Dementia is characterized by the loss of memory and other intellectual abilities that is severely enough to impede the activity of daily life [1]. Prevalence and occurrence forecasts that the number of people with dementia will continue to grow progressively. It occurs predominantly among older people and countries in demographic alteration [2]. Statistics have shown that in 2010 globally the total number of people with dementia was 35.6 million and will be expected to almost double in each 20 years, i.e., 65.7 million in 2030 and 115.4 million in 2050 [3]. In the world every year the total number of new cases of dementia is approximately 7.7 million, indicating every four seconds one new case of dementia occurs [4].

The rate of dementia will be increased in developing countries, owing to the rapid growth in the elderly population appearing in China, India, and their South Asian and Western Pacific neighbors [5]. Europe had projected 10 million disease cases in 2010 and based on United Nation's demographic forecast in 2030 this figure will rise to 14 million [6]. Looking at these statistical data, it is visible that there is an emergent need for action. Nowadays Alzheimer disease (AD) has become a leading public health concern as the world's population ages [7]. It is predicted that by 2050, people aged 60 and over will comprise 22% of the world's population with four-fifths living in Asia, Latin America or Africa [8].

Memory is a fixed set of sequencing neural networks in the brain, with a view to encode, store and consequently recall information and past experiences [9]. Neurotransmitters play an essential role in memory, learning and behavior [10]. The neurotransmitter is released at the presynaptic terminal due to a threshold action potential or graded electrical potential. The neurotransmitters travel across the synapse to bind to a postsynaptic receptor [11]. There are various types of receptors for different

neurotransmitters, each neurotransmitter binds only to specific receptors on the postsynaptic membrane. When a neurotransmitter binds to the receptor, change either exciting or inhibiting generated in the electrical state of the postsynaptic cells [12]. Excitatory and inhibitory postsynaptic potentiality depends on the kind of neurotransmitter released. Postsynaptic potentials are referred excitatory if they increase the opportunity of occurring a postsynaptic action potential and inhibitory if they decrease this opportunity. The process of neurotransmitter can be deactivated or neutralized in a number of ways that lead to various disorders [13].

A healthy brain requires an enormous supply of neurotransmitters with a view to process thoughts and emotions to completes capacity. The right balance of neurotransmitters to function is also the major concern of brain [14]. It has usually been presumed that death of neurons causes damage of neurotransmitter, on the contrary an insufficient supply of neurotransmitter itself may lead to neurodegeneration with the end result being cognitive impairments (i.e., dementia). The furthermost common neurodegenerative disorders that present with dementia are Alzheimer's disease (AD), diffuse Lewy body disease (DLBD) and frontotemporal lobar degeneration (FTLD) [15]. More hurriedly progressive dementias have been seen with prion diseases, particularly Creutzfeldt-Jakob disease (CJD) [16]. AD is the most common form of dementia. In case of AD patients, acetylcholine (ACh), a neurotransmitter vital for memory and learning process, is decreased in both concentration and function [17].

The silent heroes of our brains are neurotransmitters. In order to function the brain properly, its cells must be able to communicate with each other. Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process [18]. Drugs interfering the CNS may work presynaptically by affecting the production, storage, release or termination of action of neurotransmitters. Statistics showed that every year prescription drugs cause over 100,000 deaths and cause severe side effects to another 1.9 million people that lead to hospitalization [19]. In USA adverse drug reactions (ADR) are now becoming the fourth principal cause of death [20]. More than 50 percent of the approved drugs in the United States were related to some type of adverse effect not identified before approval as stated by the Centre for Health Policy Research (CHPR) [21]. A study in 2011 conducted by the Agency for Healthcare Research and Quality (AHRQ) showed that among drugs that causes adverse drug events seen in the hospital setting, sedatives and hypnotics were a leading source [22]. Every medication carries some risks and memory loss is a very common side effect. There are many types of OTC medicine as well as prescription drugs that cause memory loss [23]. Therefore, the intention of this study is to show the memory loss associated with the medicines.

2. Normal Age-Related Forgetfulness

Populations are growing older in countries throughout the world. Sporadic lapses in memory are considered as a normal part of the aging process for most people, not a warning sign of serious mental decline or the onset of dementia presented in Table 1 [24].

Table 1. Differences between typical age related memory changes and dementia [25, 26]

Normal Age-Related Memory Changes	Symptoms that may Indicate Dementia
Able to function independently and pursue normal activities, despite occasional memory lapses.	Difficulty performing simple tasks (paying bills, dressing appropriately, washing up), forgetting how to do things that was completed many times.
Able to recall and describe incidents of forgetfulness.	Unable to recall or describe specific instances.
May pause to remember directions, but doesn't get lost in familiar places.	Disoriented even in familiar places, unable to follow directions.
Occasional difficulty finding the right word, but no trouble holding a conversation.	Words are frequently forgotten, misused, repeats phrases and stories in the conversation.
Judgment and decision-making ability remain same as always.	Trouble in making choices, may show poor judgment or behave in socially inappropriate ways.

The memory lapses that are seen usually among older adults and normally don't consider as warning signs of dementia is given below [27]:

□ Becoming easily blurred [27]
□ Occasionally forgetting an appointment [27]
□ Entering into a room and forgetting entrance reason [27]
□ Not being able to recover information that on the tip of the tongue [27]
□ Having worry to recalling just read the information or the details of a conversation [27]
□ Suddenly forgetting where left things that uses regularly, such as keys [27]
□ Forgetting names of acquaintances or blocking one memory with a similar one, such as calling a grandson by your son's name [27]

3. Aging, Neurodegeneration and Cognitive Disorders

Increasing age of the world's population leads to a high number of people suffering from cognitive disorders especially dementia [28]. Aging is greatly related to a number of degenerative conditions, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), atherosclerosis and myocardial infarction [29]. The chances of developing dementia increase as we get older, but in early life, it is possible to develop dementia. In fact before 65 years of age it is rare to get dementia. But the risk of developing AD doubles about every five years after the age of 65 [30]. It is projected that over the age of 65 dementia affects 1 in 14 people and 1 in 6 over the age of 80 [31]. In addition to aging several factors contribute to increase the risk of dementia, such as [32]:

□ Changes in nerve cells, DNA and cell structure [32]
□ Higher blood pressure in mid-life [32]
□ Increased incidence of heart disease and stroke [32]
□ Changes in the immune system [32]
□ Weakening of the body's natural repair systems [32]

Several studies have revealed that during life span the aging process is an outcome of progressive accumulation of harmful biochemical changes, leading to an imbalance of body regulatory systems, including hormonal, immune and neuroendocrine mechanisms [32]. It is strongly assumed that these changes can be more extreme in neurocognitive or neurodegenerative disorders. There are almost 36 million people suffering from dementia, according to the estimation of Alzheimer's disease international association (ADIA) [33]. It is projected that the number will be double every 20 years, hence in 2030 about 66 million people could be affected by dementia. At present, all over the world 26.6 million people have affected from AD and by 2050 this number could be more than 100 million [34]. Like AD the global burden of PD is also rising. In a study on the world's 10 most populous nations and Western Europe's 5 most populous nations, it was projected that the number of people with PD was raised from 4.1 to 4.6 million in 2005 by two times to 8.7 to 9.3 million in the year 2030 [35]. In Asian countries such as China, India, Indonesia, Pakistan, Bangladesh and Japan and the figure of PD patients was predicted to rise from 2.57 million in 2005 to 6.17 million in 2030 [36]. Aging is one of the most important identified risk factor for neurocognitive disorders.

4. Medicine with Risk of Memory Loss

For a long time, scientists through that forgetfulness and mental confusion are outcome of aging [37]. Nowadays scientists know that memory loss associated with as older gets older is by no means unavoidable [38]. Certain study suggested that through the life the brain can grow new neuron and reshape their connections. Alcohol, drug addiction, chronic cigarette smoking, severe stress and or depression, vitamin B_{12} deficiency, head injuries and illnesses such as Alzheimer's disease etc. are causative agents of memory loss [39]. In addition to this, many people don't understand that many commonly used and prescribed medicines also can interfere with learning and memory process [23]. In case of few medicine, it is not crystal clear, still a matter of debate and requires further research. The medicine that causes memory loss are given below:

4.1 Antianxiety Drugs (Benzodiazepines)

Anxiety is a serious mental disturbance that everyone experiences at times [40]. It is characterized by an unpleasant state of tension, apprehension or uneasiness [41]. Benzodiazepines are favored drugs for the treatment of the acute anxiety states to panic disorder, generalized anxiety disorder, social anxiety disorder, performance anxiety, post traumatic stress disorder, obsessive-compulsive disorder and the extreme anxiety sometimes encountered with specific phobias, such as fear of flying. In addition to this they are also used for treating the anxiety, muscular disorders, amnesia, seizures and sleep disorders [42]. They exert their action by binding with $GABA_A$ receptor subunits to facilitate chloride channel opening and finally membrane hyperpolarization [43]. Benzodiazepine may produce cognitive impairment like sustained attention, verbal learning and memory, psychomotor, visuo-motor and visuo-conceptual abilities due to long-term use [44]. Due to the sedative effect benzodiazepines reduce activity in key parts of the brain, including those involved in the transfer of events from short-term to long-term memory. For this reason anesthesiologists commonly used benzodiazepines for anesthesia [45].

Studies show that stoping of long-term benzodiazepine therapy causes improvement of cognitive function in the first six months, though deficits may be permanent or take longer than six months to return to baseline. Long-term benzodiazepine uses for elderly, increases the risk of cognitive impairment, but gradual withdrawal is related to improvement of cognitive functions [46]. Neuroimaging studies suggested that long-term benzodiazepine therapy causes transient changes in the brain, without any brain abnormalities. But a study establishes that benzodiazepines are connected with an increased risk of dementia and it is suggested that benzodiazepines are avoided in the elderly [47]. In fact long-term use of benzodiazepines may have analogous effect on the brain as alcohol. Benzodiazepines, in combination with antihypertensives cause dementia by affecting the cholinergic system. This type of dementia is accountable for 10 percent of patients attending memory clinics. Since a greater number of people use benzodiazepines, a small increment of memory loss might contribute significant deleterious effect of the cognitive function [48]. In a study of 1,389 people between the age of 60 to 70 years suggest that long-term use of benzodiazepines is associated with increased cognitive failure [49, 50]. Several prospective studies suggested the link between the use of benzodiazepine and its risk of cognitive impairment in the general population of various countries [50]. Examples of commonly prescribed benzodiazepines that causes memory loss are alprazolam, chlordiazepoxide, clonazepam, diazepam, flurazepam and lorazepam [51].

4.2 Hypolipedemic Drugs (Statins)

In the United States, coronary heart disease (CHD) is the leading cause of almost half of all deaths [52]. The prevalence of CHD is associated with increased levels of low-density lipoprotein (LDL) cholesterol and triacylglycerols and with low levels of high-density lipoprotein (HDL) cholesterol [53]. Alteration of hydroxymethylglutaryl coenzyme A (HMG-CoA) to mevalonate by HMG-CoA reductase is the rate-limiting step in the hepatic cholesterol synthesis. The statins are structurally similar to HMG-CoA that competitively inhibits the enzyme, HMG-CoA reductase responsible for synthesis of cholesterol [54]. In all types of hyperlipidemias statins are effective in lowering plasma cholesterol levels. Reduction of brain levels of cholesterol is probably responsible for memory impairment and loss of other mental processes associated with statins. In fact, the human brain contains a quarter of the body's cholesterol liable for the formation of connections between nerve cells which trigger memory and learning. In addition to this demyelination of CNS nerve fibers may be result of memory impairment of statins. The study showed that may be within weeks or after several years of statin therapy the onset of cognitive impairment arises [55]. In fact the median time of onset is about six months. Examples of commonly prescribed HMG-CoA reductase inhibitors that cause memory loss are atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin [56].

Higher levels of low density lipoprotein (LDL) cholesterol (i.e. >100 mg/dL) in extracellular brain increase the risk of AD by increasing the production of beta amyloid 42 (Aß42). By using the apolipoprotein E (apoE) receptor LDL cholesterol is primarily bounded within neuronal membranes and then shifted to the LDL receptor related protein, that transports LDL cholesterol into neurons. The variety of the apoE receptor generated by the ε4 allele strongly binds with LDL cholesterol to lessen its intracellular transport [57], which plays a vital role to increased intra-membranous and extracellular LDL cholesterol levels. These increased levels lead to rise the production of Aß42, probably by rising the incision of amyloid

precursor protein (APP) at extracellular (ß-secretase) and intra-membranous (γ-secretase) positions [58]. Furthermore, Aß42 itself inhibits LDL cholesterol from binding to apoE and to the LDL receptor related protein, which further increases extracellular LDL cholesterol levels and further increases Aß42 production. High density lipoprotein (HDL) can reduce increased Aß42 production by binding to LDL cholesterol even in the presence of Aß42 [58]. In this way elevated extracellular brain levels of LDL and HDL cholesterol increase and decrease AD risk, respectively and the ε4 allele of the apoE receptor further increases AD risk.

In 2012, the FDA changed the labels for statins to show their increased risk of memory loss [59]. The agency has evaluated databases that record reports of bad reactions to drugs and statins clinical trials that involved assessments of cognitive function. The report about memory loss, forgetfulness and confusion span all statins products and all age groups. Overall, the symptoms were not serious and were reversible within a few weeks after the patient stopped using the statins [60].

Several research suggested the memory loss associated with statins in various countries. A review study published in 2003 showed that out of 60 case reports of statin-related memory loss available until then 36 involved simvastatin, 23 involved atorvastatin and 1 involved pravastatin [61]. The memory loss of statins was identified within first two months of statins therapy among half of these cases. Not only that recovery of memory loss was reported for 56% of patients due to withdraw [62]. In addition to this continuing statins use cause the return of memory loss. Another one study showed the case of memory loss due to use of rosuvastatin by a 56-year old man at a dose of 10 mg/day. This short-term memory loss gradually resolved after the drug was withdrawn [56, 63].

4.3 Antidepressant Drugs (Tricyclic antidepressants)

Depression is a serious disorder that affects about 14 million adults in the US each year. The lifetime incidence rate of depression in the US has been assessed to include 16 percent of adults (21 percent of women, 13 percent of men), or more than 32 million people [64]. There are many symptoms of depression these are strong feelings of sadness, desperateness and despair in addition to the inability to experience pleasure in normal activities, variations in sleep patterns and appetite, loss of energy, and suicidal thoughts. Most clinically useful antidepressant drugs potentiate, either directly or indirectly, the actions of norepinephrine and or serotonin in the brain. Antidepressants are prescribed for major depression (backup), chronic pain, obsessive-compulsive disorder (OCD), fibromyalgia, menopausal symptoms, hypnosis, smoking cessation, sedation, bulimia etc [65].

Memory problems of TCAs (tricyclic antidepressants) are due to blockage of two important neurotransmitters, serotonin and norepinephrine [66]. Serotonin is a monoamine neurotransmitter connected to emotional and motivational aspects of human behavior, including anxiety, depression, impulsivity, sexual behavior, etc. Serotonin also has an important role in cognitive functions, including memory and learning in particular by interacting with the cholinergic, glutamatergic, dopaminergic or GABAergic systems. The study suggested that receptors of the crucial brain structures are responsible for mediating aforementioned actions of serotonin [67]. Norepinephrine is a neurotransmitter in the catecholamine family that is important for attentiveness, emotions, sleeping, dreaming, learning and memory. Study shows that emotional arousal leads to release of norepineprine in the brain by activation of the locus coeruleus, resulting in the enhancement of memory [68]. About 35 percent of adults taking TCAs report some degree of memory impairment and about 54 percent report having difficulty concentrating [69]. Examples of commonly prescribed antidepressant drugs that causes memory loss are amitriptyline, clomipramine, desipramine, doxepin and imipramine [70].

4.4 Antiepileptic Drugs (Older and newer)

Epilepsy is a disorder characterized by recurring seizures. Epilepsy is not a single entity, in fact, it is an assortment of different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive and synchronous discharge of cerebral neurons. In a study show that about 10 percent of the population will have at least one seizure in their lifetime [71]. Drugs that are useful in seizure reduction accomplish this by several mechanisms, like blockade of voltage-gated channels (Na^+ or Ca^{2+}), enhancement of inhibitory GABAergic impulses, or interference with excitatory glutamate transmission. Some antiepileptic drugs seem to have multiple targets within the CNS, whereas the

mechanism of action for some agents is unclear. The antiepilepsy drugs inhibit seizures but do not prevent epilepsy [72]. They are used for the treatment of generalized tonic-clonic seizures, partial seizures, absence seizures, myoclonic and atypical absence syndromes, status epilepticus, bipolar disorders, trigeminal neuralgia, neuropathic pain including postherpetic neuralgia. To treat seizures, these medications are used for long term and increasingly prescribed for nerve pain, bipolar disorder, mood disorders and mania [73].

Anticonvulsants limit seizures by reducing the flow of signals within the CNS and adversely affect cognitive function by suppressing neuronal excitability or enhancing inhibitory neurotransmission [74]. Impaired attention, vigilance and psychomotor speed are the main cognitive effects of antiseizure drugs, but secondary effects can apparent on other cognitive functions. In fact worsen cognitive dysfunction is reported for older antiseizure drugs (e.g., phenobarbital) than newer antiseizure drugs. The chance of cognitive decline is higher for phenytoin, although generally limited to visually guided motor functions [75]. Mild as well as significant difficulties could arise owing to the use of carbamazepine [76]. In addition to this, at low doses sodium valproate is sufficient for mimimum cognitive problems. Among the newer drugs high risk of cognitive dysfunction is associated with topiramate [77]. Examples of commonly prescribed antiepileptic drugs that causes memory loss are acetazolamide, carbamazepine, ezogabine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, topiramate, valproic acid and zonisamide [70].

4.5 Narcotic Painkillers (Opioids)

Pain is a consequence of complex neurochemical processes in the nervous system that causes unpleasant feeling [78]. Management of pain is one of clinical medicine’s greatest challenges. However, opioids are generally the drugs of choice for severe or chronic malignant or nonmalignant pain (i.e., rheumatoid arthritis) that may not respond well to other painkillers. Opioids interact stereospecifically in different parts of the body, including with protein receptors on the membranes of certain cells in the CNS, on nerve terminals in the periphery and on cells of the gastrointestinal tract and other anatomical regions [79]. The main effects of the opioids are accomplished by three major receptor families such as μ (mu), κ (kappa) and δ (delta). These drugs act by inhibiting the movement of pain signals within the CNS and by blunting one's emotional reaction to pain [80]. Both these actions are accomplished by chemical messengers that are also complicated in many aspects of cognition. Hence the use of these drugs can hamper with long- and short-term memory, particularly when used for prolonged periods of time [81]. Some common examples of prescribed opioids that produces memory loss are fentanyl, hydrocodone, hydromorphone, morphine and oxycodone [70].

4.6 Anti-Parkinson's Drugs (Dopamine agonists)

The neurodegenerative condition, Parkinson's disease (PD) is the most common cause of parkinsonism which is a progressive neurological disorder of muscle movement, categorized by tremors, muscular rigidity, bradykinesia (i.e., slowness in initiating and carrying out voluntary movements) and postural and gait abnormalities [82]. Over the age of 65 is the most potential periods of PD, among whom the prevalence is about 1 in 100 individuals [83]. Dopamine (D) receptor agonists exert their anti-Parkinson action by interacting with various D receptors. Including PD, these drugs are also used to treat certain pituitary tumors and restless legs syndrome (RLS). Anti-Parkinson's drugs activate signaling pathways for dopamine, a chemical messenger related in many brain functions, such as motivation, the experience of pleasure, fine motor control, learning and memory [84]. Consequently, serious side effects of anti-Parkinson's drugs include memory loss, confusion, delusions, hallucinations, drowsiness and compulsive behaviors such as overeating and gambling. Examples of some commonly prescribed dopamine agonists that causes memory loss are apomorphine, pramipexole and ropinirole [85].

4.7 Antihypertension Drugs (β-blockers)

Hypertension is either a sustained systolic blood pressure (SBP) of greater than 140 mm Hg or a sustained diastolic blood pressure (DBP) of greater than 90 mm Hg [86]. Elevated blood pressure is an immensely common disorder, in the United State almost 15 percent of the population is affected (i.e., 60 million people) by hypertension [87]. Albeit many of these individuals have no symptoms, chronic hypertension (i.e., either systolic or diastolic) can lead to cerebrovascular disease (i.e., strokes), congestive heart failure, myocardial infarction and renal damage [88]. Although hypertension may arise

secondary to other disease processes, over 90 percent of patients have essential hypertension, a disorder of unidentified origin affecting blood pressure-regulating mechanisms. β-blockers are suggested as first-line drug therapy for hypertension when concomitant disease is present, for example, in post myocardial infarction (MI) patients or in patients with a previous MI [89]. The β-blockers act by reducing blood pressure principally by decreasing cardiac output [90]. They may also decrease sympathetic outflow from the CNS as a result the release of renin from the kidneys is blocked, that lead to declining the formation of angiotensin II and the secretion of aldosterone. The main therapeutic effect of β -blockers are to slow the heart rate and decrease blood pressure and characteristically are prescribed for high blood pressure, hypertension, congestive heart failure, abnormal heart rhythms, arrhythmias, hypertensive emergencies [91]. They are also effective to treat chest pain (i.e., angina), migraines, tremors and, in eye drop form, definite types of glaucoma [92].

Side effects of β-blockers are thought to cause memory problems by interfering with the action of prime chemical messengers in the brain, including norepinephrine and epinephrine. Extensive evidence supporting that norepinephrine is implicated in hippocampus based learning and memory in addition to its established peripheral actions [93]. Abundant evidence indicates that epinephrine is the causative agent for emotionally arousing learning tasks after stressful stimulation. Some common examples of prescribed β-blockers that causes memory loss are atenolol, carvedilol, metoprolol, propranolol, sotalol and timolol [85].

4.8 Sleeping Aids (Nonbenzodiazepine sedative-hypnotics)

Sleeping well is very essential for physical health and emotional well-being, which is considered as the barometer of the overall health [94]. In many cases it is known that, people in good health tend to sleep well, on the contrary, those affecting from regular sleeping problems often have an underlying medical or mental health problem, it can be minor or serious. Weight gain, accidents, impaired job role and relationship are symptoms of sleep disorder [95]. Some sleep disorders can cause serious difficulties in quality of life that are enough to interfere with normal physical, mental, social and emotional functioning. Some common examples of prescribed sleeping aids are eszopicloneand and Z-drugs such as zaleplon and zolpidem. All of these groups are thought to control benzodiazepine specific subunit sites, as specific agonists of the $GABA_A$ receptors [96]. They are a group of nonbenzodiazepine drugs, but having similar effects like benzodiazepines, which are effective in the treatment of insomnia, mild anxiety and other sleep problems [97]. However, these are molecularly different from benzodiazepines, they work on many of the same brain pathways and chemical messengers, producing memory loss as well as similar serious side effects and problems with addiction and withdrawal [98]. The Z-drugs can also provoke memory loss and sometimes trigger dangerous or curious behaviors. It is supposed that the main mechanism of action of Z-drugs are mediated by α_1 hypnotic-inducing site of the $GABA_A$ receptor [85].

4.9 Incontinence Drugs (Anticholinergics and antimuscarinic)

The baby boom generation grows older and consequently urges incontinence is increasing [99]. Incontinence medications are effective to mitigate symptoms of overactive bladder and reduce incidents of urge incontinence [100]. Incontinence drugs block the action of the neurotransmitter, acetylcholine that mediates multiple functions in the body [101]. Anticholinergics inhibit involuntary contractions of the muscles that control urine flow in the bladder. They also inhibit activity in the memory and learning centers in the brain. When the drugs are administered for more than a short time or used with other anticholinergic drugs then the risk of memory loss is raised [102]. Older people are predominantly susceptible to the other adverse effects of anticholinergic drugs, like constipation (which in turn can cause urinary incontinence), blurred vision, dizziness, anxiety, depression and hallucinations. Some common examples of prescribed anticholinergics that cause memory loss are darifenacin, oxybutynin, solifenacin, tolterodine and trospium [85]. Several studies showed that memory loss associated due to the use of oxybutynin ER is comparable to about 10 years of cognitive aging. (i.e., transformed these people from functioning like 67 year olds to 77 year olds) [103].

4.10 Antihistamines (First-generation)

Histamine is a neurotransmitter that mediates a wide variety of responses, such as allergic and inflammatory reactions, dilating blood vessels, gastric acid secretion and neurotransmission in parts of the brain [104]. There are no clinical applications of histamine. Antihistamines act by acting as

an antagonist of histamine (H) receptors [105]. These medications are effective in the treatment of allergic rhinitis, urticaria, severe itching, common cold, insomnia, motion sickness and extrapyramidal symptoms, dizziness, anxiety or insomnia. On account of the anticholinergic effect of these medications (i.e., prescription and over-the-counter) they inhibit the action of acetylcholine [106]. Acetylcholine is one of the important brain's natural neurotransmitters. In the CNS, it has a number of effects, including arousal and reward, as well as learning and short-term memory (using synaptic plasticity, the ability to change neuron connection strength). It plays an important role in the formation of memories, verbal and logical reasoning and the ability to concentrate. It also offers protective benefits and may limit the neurological decay related to neurodegenerative diseases [107]. In this way first-generation antihistamines inhibit activity in the memory and learning centers in the brain, which can lead to memory loss. Some common examples of prescribed antihistamines that causes memory loss are brompheniramine, carbinoxamine, chlorpheniramine, clemastine, diphenhydramine and hydroxyzine [108].

5. Anticholinergic Burden and Memory Loss

Medicines which possess anticholinergic characteristics are commonly prescribed in the aged population for several medical conditions [109]. The cumulative effect of administering one or more medicines with anticholinergic characteristics is known to as anticholinergic burden [110]. The greater number of medicines that frequently prescribed to aged people are not regularly recognized as having anticholinergic activity and empirically physicians recommends these medicines according to their expected therapeutic benefits ignoring the risk of cumulative anticholinergic burden [111].

Numerous studies have claimed the adverse effects connected with greater anticholinergic burden. Studies have shown that anticholinergic medicines may badly affect on cognitive and physical activity [112-121] and more specifically anticholinergic burden is a robust prognosticator of cognitive and physical impairments in aged people living in both community and residential care [112-115,120,122]. The use of medicines with anticholinergic characteristics is a robust independent prognosticator of mortality in aged people as stated in a retrospective study which was conducted in Finland [123,124]. Currently, various studies in the aged population have also claimed a connection between anticholinergic manifestation and mortality with an increased risk of hospitalizations [109,114, 125 ,126].

At least 20% of the 36 million Americans who are 65 years and older are being prescribed at least 1 anticholinergic medication, either because treatment is essential for conditions such as asthma, urinary incontinence and psychiatric disorders or simply due to prescriber unaware of the long list of drugs linked to anticholinergic activity and their effects. As stated formerly, first-generation antihistamines are more simply recognized as anticholinergic delinquents, but other agents with anticholinergic properties like opoids, TCAs and incontinence drugs are doubtful to start out alarms among prescribers or possibly too among pharmacists [111].

To measure anticholinergic burden various rating scales are regularly used in research and clinical practice. According to anticholinergic risk scale (ARS) drugs are classified in the range of 1 to 3 points, in which 1 point means low risk of anticholinergic side effects, 2 points means moderate risk of anticholinergic side effects and 3 points means high risk of anticholinergic side effects [127]. Medicines with anticholinergic properties of this study are classified as per ARS in the following points specified in Table 2.

Table 2. Anticholinergic Burden of the referred medicines according to ARS [127]

Therapeutic Class	1 Point	2 Points	3 Points
Antianxiety Drugs (Benzodiazepines)	Alprazolam	-	-
	Clonazepam	-	-
	Diazepam	-	-
	Flurazepam	-	-
	Temazepam	-	-
Narcotic Painkillers	Fentanyl	-	-

(opioids)	Morphine	-	-
	Oxycodone	-	-
Antiepileptic Drugs (Older and newer)	-	Carbamazepine	-
	-	Oxcarbazepine	-
Antidepressant Drugs(Tricyclic antidepressants)	-	-	Amitriptyline
	-	-	Clomipramine
	-	-	Desipramine
	-	-	Doxepin
	-	-	Imipramine
	-	-	Nortriptyline
	-	-	Trimipramine
Antihistamines(First-generation)	-	-	Brompheniramine
	-	-	Chlorpheniramine
	-	-	Carbinoxamine
	-	-	Clemastine
	-	-	Diphenhydramine
	-	-	Hydroxyzine
Incontinence Drugs (Anticholinergics and antimuscarinic)	-	-	Darifenacin
	-	-	Oxybutynin
	-	-	Solifenacin
	-	-	Tolterodine
	-	-	Trospium

Physicians should be avoided to prescribe medications with ACh characteristics in aged patients whenever possible. They should be prescribed at the lowest dose and shortest duration possible, if considered clinically essential [128, 129]. The ACh burden can be further diminished by substituting medications having robust ACh properties with replacements, including medications with no or weak ACh properties or with nonpharmacologic interventions. The best alternative for many medications with ACh properties is to use nonpharmacologic interventions; however, this is not always possible [130, 131].

6. Medicines and their Possible Deleterious Effects on Memory and Cognitive Functions

It is well known that using illicit drugs or abusing controlled substances is harmful to the body and brain [132]. In addition to this some OTC and prescription drugs are also associated with memory loss and cognitive deficiency [133]. The more complex a drug regimen, the more difficult it may be to identify the specific drug(s) that may be causing cognitive impairment [134]. In Table 3 few medicines with their possible deleterious effects on memory and cognitive functions are presented.

Table 3. Possible Deleterious Effects of Referred Medicines on Memory and Cognitive Functions [45, 55, 66, 74, 79, 84, 93, 98, 101, 107, 108]

Therapeutic Class	Examples Generic Name (Brand Name)	Possible Deleterious Effects on Memory and Cognitive Functions
Antianxiety Drugs (Benzodiazepines) [45]	Alprazolam (Xanax), chlordiazepoxide (Librium), clonazepam (Klonopin), diazepam (Valium), flurazepam (Dalmane), lorazepam (Ativan), midazolam (Versed), quazepam (Doral), temazepam (Restoril) and triazolam (Halcion)	These medicines reduce activity in key parts of the brain, including those involved in the transfer of events from short-term to long-term memory.
Hypolipedemic Drugs (Statins) [55]	Atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol), rosuvastatin (Crestor) and	These medicines impair memory and other mental processes by depleting brain levels of cholesterol.

	simvastatin (Zocor)	
Antidepressant Drugs (Tricyclic antidepressants) [66]	Amitriptyline (Elavil), clomipramine (Anafranil), desipramine (Norpramin), doxepin (Sinequan), imipramine (Tofranil), nortriptyline (Pamelor), protriptyline (Vivactil) and trimipramine (Surmontil)	These medicines are thought to cause memory problems by blocking the action of serotonin and norepinephrine, two of the brain's key chemical messengers.
Antiepileptic Drugs (Older and newer) [74]	Acetazolamide (Diamox), carbamazepine (Tegretol), ezogabine (Potiga), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), pregabalin (Lyrica), rufinamide (Banzel), topiramate (Topamax), valproic acid (Depakote) and zonisamide (Zonegran)	These medicines are believed to limit seizures by dampening the flow of signals within the CNS.
Narcotic Painkillers (opioids) [79]	Fentanyl (Duragesic), hydrocodone (Norco, Vicodin), hydromorphone (Dilaudid, Exalgo), morphine (Astramorph, Avinza) and oxycodone (OxyContin, Percocet)	These medicines work by stemming the flow of pain signals within the central nervous system and by blunting one's emotional reaction to pain. Both these actions are mediated by chemical messengers that are also involved in many aspects of cognition.
Anti-Parkinson's Drugs (Dopamine agonists) [84]	Apomorphine (Apokyn), pramipexole (Mirapex) and ropinirole (Requip)	These medicines activate signaling pathways for dopamine, a chemical messenger involved in many brain functions, including motivation, the experience of pleasure, fine motor control, learning and memory.
Antihypertension Drugs (β-blockers) [93]	Atenolol (Tenormin), carvedilol (Coreg), metoprolol (Lopressor, Toprol), propranolol (Inderal), sotalol (Betapace) and timolol (Timoptic)	These medicines are thought to cause memory problems by interfering with the action of key chemical messengers in the brain, including norepinephrine and epinephrine.
Sleeping Aids (Nonbenzodiazepine sedative-hypnotics) [98]	Eszopiclone (Lunesta), zaleplon (Sonata) and zolpidem (Ambien)	These medicines are molecularly distinct from benzodiazepines but they act on many of the same brain pathways and chemical messengers, producing similar side effects and problems with addiction and withdrawal like benzodiazepines.
Incontinence Drugs **(**Anticholinergics and antimuscarinic) [101]	Darifenacin (Enablex), oxybutynin (Ditropan XL, Gelnique, Oxytrol), solifenacin (Vesicare), tolterodine (Detrol) and trospium (Sanctura).	These medicines block the action of acetylcholine, a chemical messenger responsible for memory as well as learning.
Antihistamines (First-generation) [107, 108]	Brompheniramine (Dimetane), carbinoxamine (Clistin), chlorpheniramine (Chlor-Trimeton), clemastine (Tavist), diphenhydramine (Benadryl) and hydroxyzine (Vistaril)	These medicines inhibit the action of acetylcholine, a chemical messenger that mediates a wide range of functions in the body. In the brain, they inhibit activity in the memory and learning centers, which can lead to memory loss.

7. Conclusion

Among all organisms the dominating characteristics of human being are due to the presence of the brain. From the present study it is clearly verified that commonly used as well as prescribed medicines are intensely connected with the risk of memory loss that's why younger and especially older population lead their life within the risk of neurocognitive disorders. Since medications are taken to save life, we will take the medicine, but marked accentuate should be given to the literature of the medicine to ensure safe and effective use. In addition to this, during prescribing physician should also consider the rational practices of drugs not the promotional materials.

Consent

It is not applicable.

Ethical Approval

It is not applicable.

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Competing Interests

Authors have declared that no competing interests exist.

Authors' Contributions

This work was carried out in collaboration between all authors. Author MSU designed the study, wrote the protocol, managed the analyses of the study and prepared the draft of the manuscript. Authors AAM and NHC managed the literature searches under supervision of author MSU. Authors MSS and MSA reviewed the scientific contents of the manuscript. All the authors read and approved the final manuscript.

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