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Memory and Cognition: Could Statin Therapy be Beneficial?

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Abstract

Following the recent more restrictive guidelines issued jointly by the American College of Cardiology (ACC) and the American Heart Association (AHA) regarding blood pressure levels, statin medicines are increasingly being prescribed for the diminution of cholesterol accumulation in arterial walls - a risk for heart disease, coronary artery disease, and stroke. Notwithstanding their side effects, this article explores whether statin medicines may also have beneficial effects on memory and cognition, particularly in Alzheimer's disease and vascular dementia.

Abbreviations

AA: Adrenergic antagonists; ACC: American College of Cardiology; ACEI: Angiotensin converting enzyme inhibitors; AD: Alzheimer's disease; ADD: AD dementia; AHA: American Heart Association; AIIRA: Angiotensin II receptor antagonists; CCB: Calcium channel blockers; CNS: Central nervous system; COPD: Chronic obstructive pulmonary disease; CSF: Cerebrospinaf fluid; CVD: Cerebrovascular disease; HDL: High-density lipoprotein; LBD: Lewy bodies dementia; LDL: Low-density lipoprotein; MCI: Mild cognitive impairment; MD: Mixed dementia; MID: Multi-infarct dementia; MMSE: Mini-Mental Status Examination; MRI: Magnetic resonance imaging; MRP: Magnetic resonance perfusion; MRS: Magnetic resonance spectroscopy; NMDA: N-Methryl-D Aspartate); NSAID: Non-steroidal anti-inflammatory drugs; PD: Parkinson's disease; PDD: PD dementia; PUD: Peptic ulcer disease; SD: Sick sinus syndrome; SNI: Sympathetic nerve inhibitors; SRD: Stroke-related dementia; SSRI: Selective serotonin re-uptake inhibitors; SVD: Subcortical vascular dementia; TBI: Traumatic brain injury; VD: Vascular disease; VDD: VD dementia; VLDL: Very low-density lipoprotein.

Keywords

Alzheimer's disease dementia; cholesterol; cognition;

memory; statins; vascular dementia.

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In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) jointly issued a new calculator of cardiovascular risk with associated new guidelines (see New England Journal of Medicine, issue of November 2013). These guidelines were criticized by many cardiology practitioners on several grounds such that, in particular, they "put millions more people on statins...without helping them feel better, live longer, and have less heart disease", etc. Indeed, the new guidelines would add nearly 13 million people to those already receiving or eligible for statin drugs; this includes about half of all people under age 40-75 and, among people aged 60-75, 87% of men (up form 30% now) and 53% of women (up from 21% now). Notwithstanding such criticisms, and overlooking for now their side effects, could not statins offer beneficial effects on brain function (particularly, memory and cognition) by their very effect of partly clearing blood vessels of cholesterol and allowing more blood to flow therein? It is the purpose of this article to begin to explore such a possibility. I start by elucidating the relationship between cholesterol and statins.

On cholesterol and statins

Cholesterol is a waxy, fat-like substance found in all body cells, insulating nerve fibers. It is needed by body cells to work properly. It exists in each cell's outer layer, maintaining the cell's membrane. It is also involved in hormonal production. Lastly, it is significant in the metabolism of certain vitamins, including vitamins A, D, and E.

Made by the liver, cholesterol travels through the blood on proteins called lipoproteins: low density lipoprotein (LDL) (aka as "bad" or "lethal" cholesterol) and high density lipoprotein, (HDL) (aka "good" or "heroic" cholesterol). A high LDL leads to a build-up of cholesterol in the arteries. Too much cholesterol in the blood can stick to arterial walls and narrow or even block them - a risk for heart disease, coronary artery disease, and stroke. Total cholesterol is equal to the sum (LDL + HDL). The cholesterol ratio is the fraction: total cholesterol/ HDL = 1 + (LDL/HDL). It is desired that this ratio be less than 3.5, that is, (LDL/HDL) < 2.5.

One also speaks of very low density lipoprotein (VLDL) (also a "bad" cholesterol). Note that VLDL and LDL are different in that VLDL mainly carries triglycerides whereas LDL mainly carries cholesterol. On the other hand, HDL carries cholesterol from other parts of the body back to the liver to be removed from the body.

A linear relationship has been demonstrated between cholesterol in the blood and beta-amyloid plaques in the brain. The higher the LDL levels, the more abundant the plaques. By contrast, the higher HDL levels could possibly prevent the accumulation of the plaques. While statins are usually employed to lower the LDL levels, regretfully, there is no medication that can increase the HDL levels.

Higher HDL levels have the following potential benefits:

- Protecting the arteries in the brain and, thereby, lessening the chances of stroke and arterial damage;
- Preventing the accumulation of amyloid-beta plaques; and
- Having an anti-inflammatory or anti-oxidant effect on the brain's neurons.

Statins and statin combinations

Statins are the most common medicines used to treat high cholesterol. They work by inhibiting the liver enzyme reductase (HMG CoA), an enzyme the body needs to produce cholesterol. As a result, LDL levels in

the blood go down, thereby lowering total blood cholesterol levels. Statins may also be combined with other cholesterol medicines such as fibric (phenoxyisobutyric) acid derivatives, bile acid sequestrants, or nicotinic acid into one pill.

Not less than seven statins and four statin combinations (a total of eleven drugs) in different doses, are dispensed. This makes up for a large variety of prescription pills which are heavily marketed, representing in the U.S. an annual market of $ 26 billion and climbing. The corresponding names are:

Generic name	Brand name
1. Atorvastatin	Lipitor
2. Fluvastatin	Lescol
3. Lovastatin	Altoprev, Mevacor
4. Pitavastatin	Livalo
5. Pravastatin	Pravachol
6. Rosuvastatin	Crestor
7. Simvastatin	Zocor

(Note: Probucol has been removed from the market in the U.S. and Canada but remains in clinical use in Asia)

Table 1: The seven types of statins

Generic name	Brand name
1. Atorvastatin + Amlodipine (a calcium channel blocker)	*Caduet*
2. Lovastatin + Niacin (nicotinic acid)	*Advicor*
3. Simavastatin + Ezetimibe (a cholesterol absorption inhibitor)	*Vytorin*
4. Simvastatin + Niacin (nicotinic acid)	*Simcot*

Table 2: The five types of statin combinations

The main reason usually evoked for the widespread prescription of statins is "to reduce the likelihood of a heart attack, stroke, or death". However, in place of this primary goal (or "real end point"), the pharmaceutical industry and the medical establishment use an intermediate measurement thought to correlate well with it. That is, lowering blood cholesterol, a "surrogate end point" and a proxy for improving patient outcomes. The thesis is that for each percentage point that LDL is lowered, there would be about 1 percent reduction of heart attacks. So these two end points (blood cholesterol level and heart attack) should track very closely. Unfortunately, that is not the case!

Primary benefits of statins

Primary benefits of statins have been mostly investigated in the case of patients with heart disease. For them, the following primary effects have been established:

- LDL (bad cholesterol) levels can be substantially lowered (apparently by 18%-55%);
- HDL (good cholesterol) levels can be increased (apparently by 5%-15%); and
- VLDL (triglyceride) levels can be reduced (apparently by 7%-30%).

The statin benefit will be greater in those individuals who have already manifested heart disease. The use of statins in this situation could be justified. However, while most patients medicated with statins will have great blood test results, only 1% of them will actually benefit (those who have no history of heart disease but may, according to prevailing conventional norms, be at risk for developing such a condition). In a large-scale (enrolled cohort of 17,800 patients), randomized, double-blind, placebo-controlled clinical trial with Crestor performed under the most rigorous conditions, the reduction was 4% for the placebo group and 2% for the Crestor population, a statistically significant result. However, a meta-analysis by the Cochrane Collaboration of all the data from 14 randomized trials and over 34,000 patients concluded that "there was no net overall benefit of statins for patients without preexisting heart disease".

Side effects of statins

Like with many medicines, the use of statins or statin combinations is accompanied by a number of side effects. Patients can either not feel or not tolerate some or all of the following minor side effects:

- **Muscle aches (not severe pain);**
- **Upset stomach;**
- **Feeling of tiredness;**
- **Headache; and**
- **Higher risk of type-2 diabetes in people already at high-risk of diabetes.**

Statins may also cause abnormal results on liver enzymes tests, but actual liver damage is very rare. Serious side effects of statin medicines are more likely when higher doses are used, including:

- Trouble breathing;
- Swelling of the face, lips, tongue, or throat;
- Hives;
- Liver problems;
- Diabetes;
- Symptoms of rhabdomyolysis (a rare muscle problem);
- Severe muscle pain, tenderness, or weakness;
- Dark-colored urine; and
- Temporary memory problems.

I opined elsewhere (Fymat, 2017) that while reportedly reducing LDL levels, increasing HDL levels, and reducing triglycerides provide great satisfaction to doctors and patients alike, it gives them a false sense of safety. Further, while most patients medicated with statins will have great blood test results, only one percent of them will actually benefit - those who have no history of heart disease but may, according to prevailing conventional norms, be at-risk of developing such a condition. The statin benefit will be greater in those individuals who have already manifested heart disease. Indeed, in such a case, some physicians even consider that statins are no less than "miraculous drugs"!

Possible memory and cognition benefits of statins

Notwithstanding the above-listed risks associated with the use of statins, do these medicines possibly offer other beneficial effects, particularly regarding memory and cognition in neurodegenerative disorders?

Can medication help slow memory loss?

How memories are formed has been a puzzle that has perplexed researchers for over a century, and there are still many questions that remain about the biological mechanisms that underpin them. Perhaps because of this gap in understanding, there are no pharmacological interventions that can be taken to improve memory and few medications are available to help manage memory loss. The severity of a person's memory loss and the underlying cause will indicate the most suitable drug therapy. Nonetheless, at present, no drug treatment can effectively cure memory loss although certain medications can help individuals ease the symptoms and manage the condition's progression.

Let us first review the available pharmacotherapy allegedly available for memory improvements.

Psychopharmacotherapy for Alzheimer-type and other dementias

In an earlier article (Fymat, 2014), I reviewed the pharmacotherapy prescribed for Alzheimer's disease (AD) and Alzheimer's disease dementia (ADD). Table 3 summarizes memory loss medications, including drug information and side effects.

Generic/brand name	Drug type	Drug indication	Side effects

Aducanumab/ Aduhelm*	o Monoclonal antibody => Biologic drug comprising living cells. It destroys plaques of toxic beta-amyloid protein	o First-line treatment for early stage AD or ADD => May be prescribed for MCI => Withdrawn from market	o Delirium o Edema o Falls o Hypersensitivity o Immunogenicity
Donepezil/ Aricept	o Cholinesterase inhibitor	o ADD =>Can be prescribed off-label for: o PDD o LBD o VDD o TBI	o Anorexia o Diarrhea o Edema o Fatigue o Hyper/hypotension o Insomnia o Muscle cramps o Nausea o Vomiting
Donepezil+Memantine/ Namzaric	o Cholinesterase inhibitor + Glutamate regulator	o Moderate-to-severe memory loss due to AD	o Anorexia o Breathing difficulty o Diarrhea o Seizure o Slow heartbeat o Urinary hesitancy
Galantamine/ Razadyne	o Cholinesterase inhibitor	o ADD	o Atrioventricular blockage o Gastrointestinal bleeding o Headache o Low appetite o Sinus bradychardia o Skin reactions o Slow heart rate o Stomach ulcer o Weight loss o Other common side effects
Lecanumab/ Leqembi	o Monoclonal antibody	o ADD	
Rivastigmine/ Exelon	o Cholinesterase inhibitor	o ADD o PDD	o General irritability o Increased risk of death from long-term use o Involuntary movements o Muscular contractions o Sleep disturbances o Tremors
Memantine/ Namenda	o Glutamate regulator and NMDA receptor antagonist	o Moderate-to-severe memory loss due to AD	o Confusion o Constipation o Dizziness o Headache o High stomach acid level

Reference: Fymat (2024)

(***Note:** Some hail human monoclonal antibodies that clear beta-amyloid deposits from the brain as the first disease-modifying treatments for the condition. However, they are not without controversy such as the one concerning the FDA-approved Aducanumab and Lecanumab despite a lack of evidence for their efficacy and concerns about their adverse effects.)

Table 3: Memory loss medications, including drug indication and side effects

- Cholinesterase inhibitors: These medications can manage various conditions affecting memory, including AD and PD. They work by blocking the enzyme cholinesterase from

breaking down acetylcholine, which is a chemical messenger that plays a vital role in memory and learning. Increasing the levels of acetylcholine in the brain can help maintain memory and delay worsening symptoms. They are the first choice treatment for memory loss. The treating physician may also prescribe the single-dose drug combination (cholinesterase inhibitor + glutamate regulator) to treat moderate-to-severe memory loss.

- Glutamate regulators: Glutamate regulators control the amount of glutamate in the central nervous system (CNS) to an optimal level. Glutamate is the most common neurotransmitter in the brain. It can excite nerve cells to their death through a process known as 'excitotoxicity'. Excitotoxic cell death can cause neurodegenerative conditions that affect memory. One example of a glutamate regulator is Memantine (Namenda), an NMDA (N-Methryl-D Aspartate) receptor antagonist that stops calcium from invading the neurons and causing nerve injury. Due to their minimal side effects, glutamate regulators may be prescribed either alone or alongside a cholinesterase inhibitor.
- Combined cholinesterase inhibitor and glutamate regulator drug: Combining the two classes of drugs is more effective than using only one medication. While superior to single drug therapy, the combination can complicate treatment plans for patients and their caregivers.

Currently, there are no specifically approved drugs for improving memory formation. While some prescription medications are used to improve memory in conditions like AD, they are not recommended for general memory enhancement in healthy adults.

Table 4 summarizes the psychopharmacotherapy for Alzheimer-type and other dementias. It is worth noting that statins are not included therein:

Pathology	**Drugs**	**Precautions**	**Side effects**
Memory problems (Monitored over an 8-week course)	Provide no cure: o Cholinesterase inhibitors*: Donepezil (Aricept®), Rivastigmine (Exelon®), Galantamine (Razadyne®) o Glutamate regulators: - Memantine (Namenda®): o Used in combination with anti-cholinesterase - N-Methyl D-Aspartate (NMDA) receptor blockers o Folate or Vitamin B-12 o Blood pressure medications	o Symptoms may worsen if the treatment is stopped or after treatment o Periodic evaluation of the treatment is required o May cause increase in cardiovascular-related events	o Aggression o Diarrhea o Dizziness o Difficulty sleeping with very vivid dreams (when taken at bedtime) o Fainting spells in people with heart problem(s) o Gastro-intestinal upset o Hallucinations o Muscle cramping o Nausea o Slow heart rate o Vomiting o Weight loss o No benefit o No clear causal link with dementia o No improved outcomes
Behavioral symptoms	o Environment change, physical exercise, avoiding triggers that cause sadness,		o Agitation o Anxiety o Irritability

	socializing with others, engaging in pleasant activities o Antipsychotics:		o Not usually recommended due to little benefits, side effects, increased risk of death
Depression	o Behavioral therapy and/or medications o Selective serotonin re-uptake inhibitors (SSRI): - Citalopram** (Celexa®) - Escitalopram (Lexapro®) - Fluoxetine (Prozac®) - Paroxetine (Paxil®) - Sertraline** (Zoloft®)		
Anxiety & Aggression	o Medications		Can be caused by several factors: o Confusion o Depression o Disorientation o Frightening o Hallucinations o Medical conditions (such as difficulty urinating or severe constipation) o Misunderstanding o Paranoid delusions o Sleep: disorders, Reduced altered sleep/wake cycles o Other causes of physical pain or discomfort
Sleep problems	o Medications or/and behavior changes o Benzodiazepines (Diazepam) and non-benzodiazepine hypnotics To be avoided: o Ramelteon, Trazodone		o Increased cognitive impairment o Falls: Increased o Worsened confusion o Little evidence to improve sleep in dementia patients
Pain	o Medications		o Ambulation decrease o Appetite impaired o Cognitive impairment exacerbated o Falls o Functional implications profound o Functional psychosocial implications o Mood depression o Quality of life implications o Sleep disturbances
Eating difficulties	o Assisted feeding, gastrostomy, feeding tube		o Abdominal pain o Aspiration risk o Complications (local) o Diarrhea o Fluid overload

			o Pressure ulcers

Reference: Fymat (2024)

Table 4: Psychopharmacotherapy for Alzheimer-type and other dementias

Precautionary notes:

1/ Donepezil should be used with caution in people with:

(a) Cardiac problems: heart disease, cardiac conduction disturbances, chronic obstructive pulmonary disease (COPD), severe cardiac arrhythmias;

(b) Asthma;

(c) Sick sinus syndrome (SSD);

(d) Peptic ulcer disease (PUD) or taking non-steroidal anti-inflammatory drugs (NSAID); and (e)

Predisposition to seizures.

2/ Sertraline and Citalopram do not reduce symptoms of agitation compared to placebo and do not affect outcomes.

Treatment with cholesterol-lowering medications

In earlier studies in animals and humans, researchers found that lowering cholesterol levels with statins not only decreases the risk of heart disease and stroke, but also seems to have a positive impact on brain function and reduce the risk of AD.

There is increasing evidence that nonsteroidal and cholesterol lowering medications may be associated with a delay in the onset of AD. There is separate evidence that beta-amyloid (1-42) is involved in the pathophysiology of AD and levels of beta-amyloid (1-42) in the CSF of AD patients are significantly lower than those found in controls. It has been suggested that these standard medications may have indirect effects that alter the normal course of AD, but there is no data to directly support this contention in humans.

Case of AD dementia

Treatment with cholesterol-lowering medications, specifically statins, is reportedly associated with up to a 73% reduction in the prevalence of AD, suggesting a potentially promising role for statins in the prevention of AD. I will review below the 14 currently-listed corresponding clinical trials indicated in clinicaltrials.gov. These are chronologically listed as per the last update posted by their corresponding authors, dating back to year 2006.

In the following descriptions, the following abbreviations have been used: [C]: Completed; [N]: New; [NAR]: Not actively recruiting; (NYR): Not yet recruiting.

[C] - Lipitor as a Treatment for Alzheimer's Disease

ID: NCT00024531

Sponsor: National(U.S.) Institute on Aging

Last update posted: 2006-11-09

Brief description: This study is a phase II, placebo controlled, double-blind, one-year trial investigating the effect of Atorvastatin calcium in the treatment of possible or probable AD. The purpose is to assess the clinical benefit of Lipitor in the treatment of AD.

[C] The Effect of Short-Term Statins and NSAIDs on Levels of Beta-Amyloid, a Protein Associated With Alzheimer's Disease

ID: NCT00046358

Sponsor: (U.S.) National Institute of Mental Health

Last update posted 2008-03-04

Brief description: There is increasing evidence that nonsteroidal and cholesterol lowering medications may

be associated with a delay in the onset of AD. The purpose of this study was to determine whether short-term combined use of the drugs Ibuprofen and Lovastatin affects levels of beta-amyloid protein in people who are at-risk for developing AD. The underlying hypothesis is that CSF beta-amyloid (1-42) levels may serve as an early biomarker of AD. Any pharmacologically induced change in it might have profound implications for the eventual onset of illness. Therefore, the study evaluated the short-term effects of these two commonly prescribed medications on the levels of CSF in a group of normal controls at-risk for developing AD.

[C] Cholesterol Lowering Agent to Slow Progression (CLASP) of Alzheimer's Disease Study
ID: NCT00053599
Sponsor: (U.S.) National Institute on Aging
Last update posted: 2009-07-28

Brief description: The CLASP trial tested the link between using a cholesterol-lowering medication and slowing disease progress in people with mild-to-moderate AD. This study specifically investigated the safety and effectiveness of Simvastatin to slow the progression of AD.

[C] Do HMG CoA Reductase Inhibitors Affect A-beta Levels?
ID: NCT00303277
Sponsor: Seattle Institute for Biomedical and Clinical Research, Seattle
Last update posted: 2010-04-13

Brief description: Studies have suggested that statins decrease the risk of AD by up to 70%, the effects differing on the specific statin used. This study compared two statins: *Simvastatin* (which crosses the blood-brain barrier (BBB) and *Pravastatin* (which does not), with respect to their ability to alter blood and cerebrospinal fluid (CSF) levels of AD and inflammatory markers. The primary aims of this study were: (1) to determine whether there is a reduction in A-beta with statins, and (2) whether the ability of the statin to cross the BBB will affect its ability to decrease A-beta. Broad implications for the treatment and prevention of AD could follow if it can be demonstrated that statins alter AD-associated biomarkers.

[C] Clinical Study of Pitavastatin Treatment for a Group of Mild-to-Moderate Alzheimer's Disease (PIT-ROAD)
ID: NCT00548145.
Sponsor: Osaka University, Osaka, Japan
Last update posted: 2012-06-14

Brief description: Some studies suggest that statin medications may be effective against AD. However, this has not been proven. The purpose of this study was to evaluate the efficacy of Pitavastatin in patients with mild-to-moderate AD and hypercholesterolemia.

[C] Effects of Simvastatin on Biomarkers (SimBio)
ID: NCT01142336
Sponsor: University of Washington
Last update posted: 2017-07-28

Brief description: This is a double-blind, placebo-controlled trial of Simvastatin to see if it produces beneficial changes in cerebral spinal fluid proteins associated with AD. These molecules are thought to be important in the development of AD.

[C] - Dosage and Efficacy of Probucol-induced apoE to Negate Cognitive Deterioration (DEPEND)
ID: NCT02707458
Sponsor: Douglas Mental Health University Institute
Last update posted: 2018-01-31

Brief description: DEPEND is an open-label is a patient-centric but dosage-masked trial of the retired cholesterol-lowering drug Probucol as an agent to increase availability of apolipoprotein E (apoE) in the CSF of cognitively intact older persons at-risk of AD

dementia. Limited human data suggest that higher plasma and CSF concentrations of this statin result in stronger increases in CSF apoE concentration. The aim of DEPEND was to develop an individualized dosing regimen that will result in plasma concentrations that are likely to increase CSF apoE concentration by 50%.

[C] - Evaluating Simvastatin's Potential Role in Therapy (ESPRIT)

ID: NCT00486044

Sponsor: University of Wisconsin, Madison

Last update posted: 2019-03-05

Brief description: Some studies suggest that statins may help prevent AD. However, this has not been proven in humans. The purpose of this study was to investigate whether Simvastatin affects processes related to the development of AD, including: (1) levels of beta-amyloid-42 found in the spinal fluid surrounding the brain, (2) blood flow in the brain, (3) inflammation in the brain, and (4) cognitive function.

[C] Endothelial Facilitation in Alzheimer's Disease

ID: NCT01439555

Sponsor: University of Massachusetts, Worcester

Last update posted: 2019-07-30

Brief description: Patients with mild AD will be given three different drugs (Simvastatin, L-Arginine, and Tetrahydrobiopterin) to increase the blood flow to the brain, and improve blood vessel and brain function. Each drug can help to open the blood vessels in the brain, and together they may be more effective than each drug alone. The hypothesis was that small blood vessels secrete substances that maintain the integrity of the brain, and may prevent loss of nerve cells leading to AD.

[C] Statin Effects on Beta-Amyloid and Cerebral Perfusion in Adults at Risk for Alzheimer's Disease (SHARP)

ID: NCT00939822

Sponsor: University of Wisconsin, Madison

Last update posted; 2019-08-09

Brief description: Beta-amyloid is found in the brain and in the liquid around the brain and spinal cord. High amounts of beta-amyloid may be associated with a greater risk of getting AD. The primary aims of this study were: (1) to investigate whether Simvastatin can lower the amount of beta-amyloid in the spinal fluid, and (2) if it affects memory and thinking, blood flow in the brain, and blood vessel function.

[C] - Cerebral and Peripheral Perfusion Pilot Study (CAPP)

ID: NCT00751907

Sponsor: University of Wisconsin, Madison

Last update posted: 2019-09-09

Brief description: In order to better understand the mechanisms through which statins may possibly modify blood AD risk, this study evaluated the hypothesis that in middle-aged, asymptomatic, adult children of persons with AD, Atorvastatin therapy will beneficially affect mechanisms thought to contribute to AD risk by: (1) improving blood flow in the brain, (2) improving cerebral perfusion, (3) increasing brain activity patterns, and (4) improving blood vessel function. The study evaluated blood flow in the brain (measured by MRI) and blood vessel function (measured by ultrasound).

[C] - To Evaluate the Safety and Effectiveness of Atorvastatin Plus a Cholinesterase Inhibitor in AD Patients

ID: NCT00151502

Sponsor: Viatris Inc. (a merger of Pfizer's Upjohn and Mylan)

Last update posted: 2021-02-18

Brief description: The purpose of this study was to find out whether Atorvastatin taken with a cholinesterase inhibitor was effective for treating AD.

[ANR] - Statins in Reducing Events in the Elderly Mind (STAREE-Mind) Imaging Substudy

ID: NCT05586750

Sponsor: Monash University, Australia

Last update posted 2023-07-27

Brief description: This study - a sub-study nested in the Statins in Reducing Events in the Elderly (STAREE) – is a double blind, randomized, placebo-controlled trial to investigate whether statins can prolong good health and maintain independence amongst older people. It examined the effect of statin treatment over a 4-year period, compared with placebo, on markers of brain health.

[N], [NYR] Statins, Cholesterol, and Cognitive Decline in Alzheimer's

ID: NCT06635252

Sponsor: Karolinska Institutet, Sweden

Last update posted: 2024-10-10

Brief description: Disturbances in brain cholesterol homeostasis may be involved in the pathogenesis of AD. Lipid-lowering medications could interfere with neurodegenerative processes in AD through cholesterol metabolism or other mechanisms. This study posits that: "(1) … disturbances in brain cholesterol homeostasis may be involved in the pathogenesis of AD; (2) Lipid-lowering medications could interfere with neurodegenerative processes in AD through cholesterol metabolism or other mechanisms; (3) Investigating the causal effect of statins on cognitive function as measured by MMSE; and (4) identifying the mediating or modifying effect of cholesterol between statins and cognitive function in patients with AD".

Case of vascular dementia

Recent evidence suggests that there is a significant overlap between AD and cerebrovascular disease (CVD). In fact, AD and cerebrovascular disease may decline sharply amongst those over 70-75 years of age. Insufficient patients of this age group have been share some of the same risk factors, including hypercholesterolemia.

Remember that vascular dementia (VD) is dementia caused by a series of strokes. Similar to the restricted blood flow due to cholesterol deposits, the restricted blood flow due to strokes likewise reduces oxygen and glucose delivery to the brain, causing cell injury and neurological deficits in the affected region. VD is at least partially preventable. Whereas ischemic changes in the brain are irreversible, periods of stability or even mild improvement do occur.

Subtypes of vascular dementia include:

- Subcortical vascular dementia (SVD): It occurs from damage to small blood vessels in the brain.
- Multi-infarct dementia (MID): It results from a series of small strokes affecting several brain regions.
- Stroke-related dementia (SRD): It involves successive small strokes, causing a more gradual decline in cognition; and
- Mixed dementia (MD).

Prevention of strokes is attempted through reduction of stroke risk factors, such as high blood pressure, high blood lipid levels, atrial fibrillation, or diabetes mellitus. Medications for high blood pressure include: Adrenergic antagonists (AA); angiotensin II receptor antagonists (AIIRA); angiotensin converting enzyme inhibitors (ACEI); and sympathetic nerve inhibitors (SNI).

Statin therapy has been shown to reduce the risk of vascular events in younger individuals with manifest atherosclerotic disease or at high-risk of vascular events. However, data derived from meta-analyses of existing trials suggests that the efficacy of statins may included in major trials to be certain of the benefit. Within this age group part of the benefit of statin

therapy may be offset by adverse effects including myopathy, development of diabetes, cancer and cognitive impairment, all of which are more prevalent in the elderly in any event. Consequently, the use of statins in the over 70 age group raises fundamental questions about the purpose of preventive drug therapy in this age group. When a preventive agent is used in the context of competing mortality, polypharmacy and a higher incidence of adverse effects of its use should be justified by an improvement in quality of life or some other composite measure that demonstrates that the benefit outweighs other factors.

Nonetheless, a comprehensive review study by Goldstein et al. (2023) aimed to evaluate contemporary evidence that either supports or refutes the conclusion that aggressive LDL cholesterol lowering or lipid lowering exerts toxic effects on the brain, leading to cognitive impairment or dementia or hemorrhagic stroke. It found that *"the preponderance of observational studies and data from randomized trials do not support this conclusion"*. Specifically:

- Statin therapy was ineffective in treating or preventing stroke or dementia″. In people without a history of cerebrovascular disease (CVD), the risk is nonsignificant;
- Achieving very low cholesterol LDL levels does not increase that risk″; and
- Data reflecting the risk of hemorrhagic stroke with lipid-lowering treatment among patients with a history of hemorrhagic stroke are not robust and require additional focused study″.

Whereas, as just stated, the Goldstein's et al. review excluded any stroke risk by cholesterol therapy, it remains to investigate whether statin therapy could be beneficial in countering memory impairment and improving cognition in stroke and other patients. For this therapy, only two clinical trials are listed in clinicaltrials.gov, as indicated below:

[C] Statins in Cerebral Blood Flow and Neuronal Activity--A Pilot Study
ID: NCT03411291
Sponsor: Cedars-Sinai Medical Center< Los Angeles
Las update posted: 2018-02-19

Brief description: A number of recent studies suggests that statins, typically used to lower blood cholesterol have an effect on the brain. Patients treated with statins may have increased blood flow in the brain resulting in increased activity of the brain's neurons. The neuronal system is linked to memory. Brain MRI with MRS and magnetic resonance perfusion (MRP) were used to assess changes in neuronal activity in patients receiving statins vs. patients not receiving statins.

[ANR] A Clinical Trial of STAtin Therapy for Reducing Events in the Elderly (STAREE)
ID: NCT02099123
Sponsor: Monash University, Australia
Last update posted: 2024-11-21

Brief description: This study examined whether treatment with statin (Atorvastatin 40mg) will prolong disability-free survival and reduce major cardiovascular events amongst healthy elderly people (≥70 years).

All of the above clinical trials are summarized in Table 4 below:

ID: NCT	Statin	Other drug combination	Purpose	Outcome measure(s)
00024531	Atorvastatin	None	Clinical benefit in treatment of probable or possible AD	Not specified
00053599	Lovastatin	Ibuprofen	Effects on CSF levels of A-beta-levels	Unspecified
00303277	Simvastatin	None	Slowing down AD progression	1- CSF A-beta levels 2- CSF biomarkers
00548145	Simvastatin	Pravastatin	Effect of ability to cross BBB	1- Cognitive assessment (Japanese scale) 2- MMS-NPI 3- Zarit burden scale 4- Physical self-maintenance
02707458	Pitavastatin	None	Efficacy on mild-to-moderate AD and hyper-cholesterolemia	1- Plasma concentration of Probucol 2- ApoE concentration in CSF
00486044	Simvastatin	None	Beneficial changes in cerebral spinal fluid proteins associated with AD	1- Change in CSF-Abeta-42 2- Change in regional CBF on MRI 3- Change in inflammatory markers 4- Change in cognitive performance
00939822	Probucol	None	Increased apoE availability in the CSF of cognitively intact older persons at-risk of ADD	1- CSF change + Abeta-42 levels as measured by MAP 2- CSF change + Abeta-40 levels as measured by MAP as measured by DUPLEX 3- CSF (sAPP-alpha) + CSF (sAPP-beta) as measured by DUPLEX 4- CSF changes in total-tau as measured by MAP
00751907	Simvastatin	None	Effects on A-beta 42 in spinal fluid surrounding the brain; blood flow and inflammation in the brain; and cognitive function	1- Change in rCBF 2- Change in endothelial function
00151502	Simvastatin	L-Arginine + Tetrahydro-biopterin	Blood flow increase in brain; blood vessel improvement; and brain function	1- Efficacy for human use in AD treatment 2- Efficacy for human use in daily living activities
05586750	Simvastatin		Beta-amyloid lowering in the spinal fluid; effects on memory and thinking; blood flow in the brain; and blood vessel function	1- Free water 2- White matter hyperintensity volume 3- Cortical thickness 4- Hippocampal volume 5- Microbled and lacunae 6- Prefrontal cortex cerebral perfusion 7- Whole brain white matter fractional anisotropy 8- Perivascular space volume
06635252	Atorvastatin	None	Improvements in blood flow in the brain; cerebral perfusion; increase in brain activity patterns; blood	Cognitive decline

			vessel function	
03411291	Atorvastatin	Cholinestarase inhibitor	Effective AD treatment	1- MRS 2- MRI perfusion
00046358	Unspecified	None	Prolong good health; maintain independence amongst older people	Intervention treatment with: 1- Lovastatin 2- Ibuprofen
01439555	Unspecific	Unspecific	Disturbances in brain cholesterol homeostasis; involvement in AD pathogenesis; interference with neurodegenerative processes; causal effect of statins on cognitive function; identification of mediating mechanism or modifying effect	1- Change in cerebral flow (MRI) 2- Change in cerebral blood flow by ASL during MRS 3- MMSE score + CAST 4- ADAS-COG (original and modified versions) 5- CII-CI
01142336	Unspecific	Unspecific	Changes in neuronal activity in VD	1- Change in CSF Abeta 2- Change in CSF total tau - Change in CSF ptau181
02099123	Atorvastarin	None	Whether treatment will prolong disability-free survival and reduce major CV events amongst healthy elderly (≥70 years).	1- Composite cardiovascular health 2- Non-fatal myocardial infarction 3- Non-fatal stroke 4- Cognitive impairment 5- Dementia

Key: Abeta: Amyloid-beta; AD: Alzheimer's disease; ADAS-COG: AD Assessment Score-Cognitive; ADD: AD dementia; ASL: Arterial Spin Labeling; BBB: Blood-Brain Barrier; CAST: Cognitive Assessment Screening Test; CBF: Cerebral Blood Flow; CDRS: Clinical Assessment Screening Test; CII-CI: Clinical-based Interview Impression plus Caregiver Input; MAP: Multi-Analyte Profining; MMSE: Mini-Mental Status Exam; MRF: Magnetic Resonnce Perfusion; MRI: Magnetic Resonance Imaging; MRS: Magnetic Resonance Spectroscopy; NPI: NeuroPsychiatric Inventory; r-CBF: regional Cerebral Blood Flow; s-APP: soluble-Alpha Precursor Protein; sBPP: soluble-Beta Precursor Protein); VD: Vascular Dementia

Table 4: Clinical trials addressing the potential benefits of statins on memory and cognition

Summary and conclusions

The newer blood pressure guidelines would add nearly 13 million people to those already receiving or eligible for statin drugs. Notwithstanding their side effects, it is plausible that statins could offer beneficial effects on brain function (particularly, memory and cognition) by their very effect of partly clearing blood vessels.

Statins are the most common medicines used to treat high cholesterol. They work by inhibiting the liver enzyme reductase (HMG CoA), an enzyme the body needs to produce cholesterol. As a result, LDL levels in the blood go down, thereby lowering total blood cholesterol levels.

Statins may be combined with other cholesterol medicines such as fibric (phenoxyisobutyric) acid derivatives, bile acid sequestrants, or nicotinic acid into one pill.

Not less than seven statins and four statin combinations (a total of eleven drugs) in different doses, are dispensed.

Primary benefits of statins have been mostly investigated in the case of patients with heart disease for whom low density lipoprotein (LDL) levels can be substantially lowered (apparently by 18%-55%), high density lipoprotein (HDL) levels can be increased (apparently by 5%-15%), and triglycerides levels can be reduced (apparently by 7%-30%).

Like with many medicines, the use of statins or statin combinations is accompanied by a number of side effects, which have been set forth.

Because of the gap in understanding how memory works, there are no pharmacological interventions that can be taken to improve memory and few medications are available to help manage memory loss. At present, no drug treatment can effectively cure memory loss although certain medications can help individuals ease the symptoms and manage the condition's progression.

The available pharmacotherapy reportedly available for memory improvements has been reviewed.

A comprehensive review of the use of statin therapy has excluded any stroke risk. It remains to investigate whether it could be beneficial in countering memory impairment and improving cognition in stroke and other patients.

The sidebar reproduces FDA's additional safety information for patients regarding the use of statins.

Sidebar
FDA's additional safety information for patients regarding the use of statins

On 2012-02-28, the (U.S.) FDA has approved important safety label changes for the safe and effective use of statins, including (bold-faced text is by this author):

- Patients should be aware of the following information:
  - There have been rare reports of serious liver problems in patients taking statins. Patients should notify their healthcare professional right away if they have the following symptoms: unusual fatigue or weakness; loss of appetite; upper belly pain; dark-colored urine; or yellowing of the skin or the whites of the eyes.
  - Memory loss and confusion have been reported with statin use. These reported events were generally not serious and went away once the drug was no longer being taken.
  - Increases in blood sugar levels have been reported with statin use.
  - Certain medicines should never be taken (are contraindicated) with Lovastatin (Mevacor)."
- Healthcare professionals should perform liver enzyme tests before initiating statin therapy in patients and as clinically indicated thereafter. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment, therapy should be interrupted. If an alternate etiology is not found, the statin should not be restarted.

- There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These reported symptoms are generally not serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).
- Increases in glycosylated hemoglobin (HbA1c) and fasting serum glucose levels have been reported with statin use.
- Healthcare professionals should follow the recommendations in the Lovastatin label regarding drugs that may increase the risk of myopathy/rhabdomyolysis when used with lovastatin."

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