

Adverse Effects of Statin Drugs: a Physician Patient's Perspective

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After the widely syndicated *Peoples Pharmacy* column published my experience with transient global amnesia while on a statin drug,¹ the veritable flood of emails, some 30,000, to my website (www.spacedoc.com) brought to my attention a wide range of claimed statin adverse effects, long before MedWatch became functional in this respect. People were reporting to me many different forms of cognitive dysfunction, behavioral disorders, peripheral neuropathy, amyotrophic lateral sclerosis (ALS)-like disorders, and rhabdomyolysis.

Gradually, the two faces of statins were recognized. As mevalonate pathway inhibitors, they block cholesterol synthesis, with collateral damage to both coenzyme Q10 (CoQ10 or ubiquinone) and dolichols, the cause of most side effects. As inhibitors of nuclear factor kappa B (NF- κ B), statins have both anti-inflammatory and immunomodulatory properties, probably accounting for the reduction of cardiovascular risk, while unleashing a Pandora's Box of unforeseen events.

Pharmageddon

Forty years ago Ancel Keys² sold the concept of the cholesterol etiology of cardiovascular disease, and the misguided war on cholesterol was on. Starting in the mid-1950s, anyone walking counter-current to this philosophy was considered ill-informed and seriously behind the times. I wrote thousands of prescriptions for whatever cholesterol buster was in vogue. I lectured at high schools, men's clubs, and to each of my sometimes skeptical patients on the evils of eggs, whole milk, and butter. I raised my family on no eggs, skim milk, and margarine, so convinced was I that for every 1% of cholesterol lowering, we would gain two years of productive life. Like all of my peers, I was riding the anti-cholesterol bandwagon. Who wouldn't? If you give cholesterol to rabbits,³ they get atherosclerosis. If you take cholesterol away, the atherosclerosis disappears. How much more proof is needed? Suddenly in the mid-1950s, a new disease appeared, cholesterol elevation, which was causing millions of people to die unnecessarily from heart disease and strokes.

Very few people had the slightest doubt about the information base on which this imposing cholesterol edifice was erected. None of us realized that Keys had consciously manipulated the data to include only those studies that agreed with his preconceived idea. None of us was scientist enough to know the difference between natural cholesterol of angelic disposition and its devilish oxy-cholesterol cousin, which blocked rabbit arteries with such ease.⁴ All of us were looking for better ways to lower cholesterol. Well-meaning researchers would spend their lives trying to sort out which of the many lipid components floating in

our bloodstream was the biggest enemy.

We were delighted when drug company scientists discovered the reductase step along the biochemical path to cholesterol synthesis. Suddenly we had a meaningful weapon. We had been chipping away at cholesterol for 30 years without doing much good. On the other hand, we had not done much harm either. We needed that big gun, and the billion-dollar statin industry was born! None of us even bothered to look in our dusty textbooks to find out just where this reductase step was located and what things other than cholesterol might be involved when we knocked over that one domino.

Merck had a few good men then, and they even secretly filed for a CoQ10 patent⁵ so they could combine their statins with CoQ10 "because of the inflammation to come." But then they decided to keep their worries to themselves. That should have aroused our suspicions then, but it didn't. Looking back on all this, I still feel very uncomfortable at how completely naïve I was, but in those days we all seemed to trust the drug companies as working for us. I was no different from my peers. Not only were we as doctors convinced, but we had the whole world convinced that cholesterol was our enemy. Within only a few years, millions of people were on statins.

A few patients had unusual reactions. Some of those, including me, started to research these statins, suspecting the drug company had not done its job adequately or might have tweaked the data just a bit. We found that we were right, but how could we tell the world?

Statin advertisements brought in huge revenues. Journal editors were well aware of their importance. After their drug company-sponsored "education," doctors were committed to the war on cholesterol. As a bloc they dismissed their patients' reports⁶ and the possibility of serious problems with their favorite drug, having been told nothing about this prospect in their formal continuing medical education sessions, or by the Food and Drug Administration (FDA). Young "drug reps" were carefully trained to say only what they were supposed to say. Billions of dollars were at stake.

Only in the past few years has the true legacy of statins emerged. At this point, if evidence of serious problems has been ignored, potential liability is enormous.

Metabolic Pathway

Figure 1 illustrates the critical role played by statins when they inhibit cholesterol synthesis by blocking the very beginning of the mevalonate pathway. When statins are administered in doses sufficient to compromise the synthesis of cholesterol, it is inevitable that the synthesis of CoQ10, dolichols, and other vital

biochemicals will be compromised as well.⁷ CoQ10 and dolichol insufficiency is the reason for most of our adverse reactions.

THE CAUSE OF STATIN SIDE EFFECTS

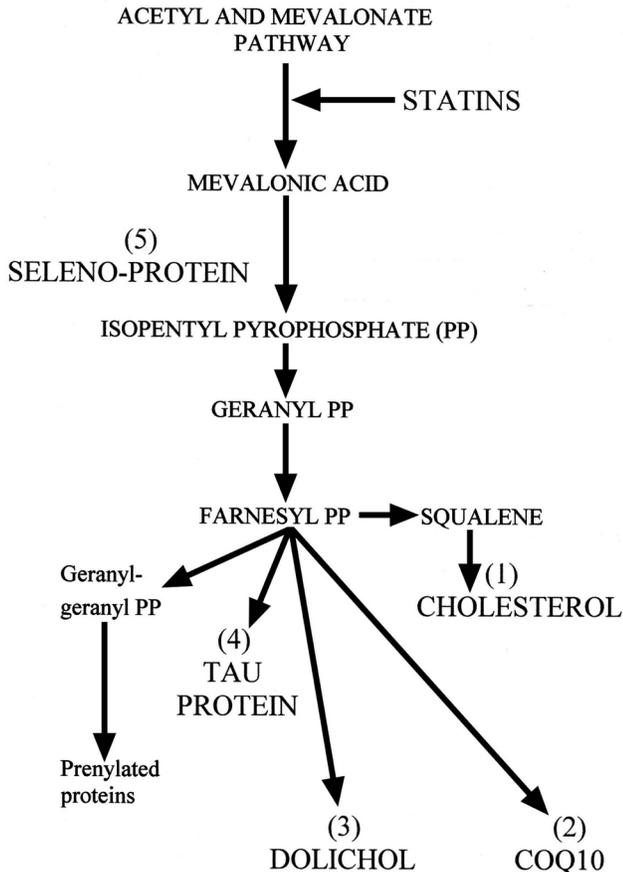


Figure 1. Acetyl and Mevalonate Pathway

Accelerated Senescence

Tens of thousands of statin users have complained to their doctors of weakness, instability, easy fatigue, muscle aches and pains, burning sensations in their extremities, depression, personality change, and faulty memory, to which their doctors generally have responded, "You have to expect this now. You are over 50" or even, "Statins do not do that."^{8, pp 8-10}

Although these experienced doctors have all pointed to a reasonable presumptive diagnosis, few have been entirely comfortable with this explanation because of a curious recurring pattern in their presentation.

All of these patients have been on statins of one brand or another, and the transition from midlife vigor to the multiple infirmities of the elderly has been much too swift in most. In the few months since the previous office visit, an aura of senescence has evolved in these patients. Doctors deal with the passage of time on a daily basis and are acutely sensitive to its telltale first traces. The complaints their patients are reporting may be common, even routine, in the elderly, yet these people are for the most part in their 60s and 70s and sometimes even much younger.

If anything out of the ordinary can be attached to these

complaints of faulty memory, weakness, and various aches and pains, it is their prematurity. These conditions ordinarily would not be seen until much later in life. Are these statin users aging prematurely, and too rapidly? If so, what could be the mechanism of expedited senescence?^{9, p18}

Mechanism of Action

Many physicians have doubted the hypothesis of cholesterol causation from the very beginning.¹⁰ We had surprising reports of studies showing benefit of statin use even when the cholesterol remained unchanged. Strangely, we observed that in almost half of the new heart attacks being reported the cholesterol levels were normal. Gradually, reports of serious adverse reactions started to accumulate: transient global amnesia, permanent myopathy, diabetes, permanent neuropathy, rhabdomyolysis, ALS, cancer, and serious neurodegenerative conditions.⁸

Evidence of another effect of statins, independent of cholesterol, began to build. The study that made a huge difference for me was a study called JUPITER.¹¹ This study selected men and women who ordinarily would not have been candidates for statins: They had cholesterol levels less than 130 mg/dL and no significant cardiovascular risk, but their inflammatory marker, high sensitivity C-reactive protein (hs-CRP), was elevated. Half of these were given a statin; the other half took a placebo. After 19 months the ethics committee forced the stopping of the study because of excess heart attacks and stroke in the placebo group. It was deemed unethical to proceed.

Naturally there was a furor of controversy about these findings, and it was in anticipation of this controversy that the study had been specially crafted. Yet two very important things emerged from this study: one was that cholesterol level appeared to have no relationship with cardiovascular disease risk, and the second was that statins did work to lower the risk level as measured by this new inflammatory marker. Doctors have been reluctant to accept this because they had accepted cholesterol causality for more than four decades. Drug companies had only to shift marketing gears a bit to account for this new reality, for statins had been proving to be powerful anti-inflammatory agents in addition to inhibitors of cholesterol synthesis, the purpose for which they originally were designed.

So it turns out that drugs designed to inhibit reductase have unanticipated anti-inflammatory and immunomodulatory properties, and it is this added feature of the drug that gives the benefit.¹² The reductase-inhibitor function blocks the reductase step in the mevalonate pathway, which synthesizes cholesterol along with CoQ10 and dolichols. The other new function is based upon the blocking of an intracellular transcriptase known as nuclear factor kappa B (NF-κB)¹³ and is independent of the mevalonate pathway.

Looking at the products made in these pathways, statins block cholesterol, considered by many to be the most important biochemical in the body, as it is especially vital for cognitive function, and also block CoQ10 and dolichols,¹⁴ which are critical to mitochondrial function. The latter mechanism is responsible for

almost all of the side effects. Additionally, statins block NF- κ B,¹⁵ giving a modest anti-inflammatory benefit to high-risk heart patients but decreasing immune status, raising the specter of increasing cancer risk. The fact that this vital information was not revealed until more than a decade after statins were marketed suggests that statins were marketed long before they were fully understood.

Reported Statin Adverse Reactions

In 2006 FDA opened the MedWatch database to those of us wishing to review for ourselves the status of statin adverse drug reports (ADRs). This has been all the more imperative since FDA has been extremely reluctant to report side-effect data on the statin class of drugs. I was first able to access MedWatch data in 2006. What follows is derived from the 2006–2013 MedWatch data. The process was not easy, for one had to review the ADRs manually. The following report is based upon atorvastatin (Lipitor) and rosuvastatin (Crestor) data using the “find” mechanism on our personal computer. This was necessary, I was told, since the appropriate software for reading MedWatch data was available only to FDA and drug company officials. The rest of us had to be content with the time-honored and accurate but painfully slow process of counting each case one by one, using the search mechanism on our own computer. Only in 2012 did MedWatch data appear in disease categories.

What prompted me to do this search, which should be FDA’s responsibility, was the email response I received, showing that most doctors were unaware of the many medical problems related to statin use.⁶ Surely many thousands of MedWatch reports must have been submitted to FDA. In many cases, I helped distraught victims make their FDA report.

Category	Search Term	Number of Reports
Cognitive	transient global amnesia (TGA)	4,691
	memory impairment	4,051
	confusion	7,973
	forgetfulness	1,304
	disorientation	2,007
	dementia	1,540
Emotional	aggressiveness	1,580
	paranoia	84
	depression	12,930
	suicidal ideation	2,348
Rhabdomyolysis	cases	10,842
	deaths	1,084
Myopathy	myalgia	17,966
	muscle weakness	8,289
	muscle spasm	9,415
	myopathy	500
Neuropathy	neuropathy	5,736
	Guillain-Barré syndrome	198
	pain in extremity	15,024
Liver	hepatitis	2,238
	liver function abnormalities	3,167
Possible amyotrophic lateral sclerosis (ALS)	unusual weakness	8,289
	balance disorders	596
	coordination abnormalities	195
	ALS	330
Diabetes	diabetes type 2	10,699
	hyperglycemia	13,073
	pancreatitis	5,725
Heart	cardiac failure	17,071
	myocardial infarction	19,371
	coronary artery occlusion	2,786
Stroke	cerebrovascular accident	12,024
	aphasia	1,230

Table 1. Number of Atorvastatin and Rosuvastatin ADRs in MedWatch, 2006–2013

The numbers in Table 1 have all have been tabulated using my categories and search terms.

There were almost 9,000 MedWatch reports in the category of severe cognitive disturbance: transient global amnesia (TGA) and memory loss. Note that confusion, disorientation, and forgetfulness are considered mild and most of the time are not reported to MedWatch. Statin-associated dementia can be diagnosed only if the patient improves after withdrawal of the statin. The cognitive manifestations of statins may be just episodes of TGA. Increasing confusion, disorientation, and forgetfulness—or progressive dementia—may resemble Alzheimer disease though differing in underlying pathology.

Short-term cognitive loss with duration measured in seconds and minutes will rarely be recognized even by the victim, and yet it might be critical to a pilot, the crew, and airline passengers. The incidence of such episodes may well be 10 times greater than that of full-blown TGA attacks. We will never know for certain. The passage of time is too short for recognition, yet special studies have revealed just how common these brief lapses can be.¹⁶

Rhabdomyolysis, an especially serious form of muscle damage, has a fatality rate of 10%, owing to the blockage of renal tubules by the muscle cell fragments from ruptured muscle cell membranes. Although cerivastatin (Baycol) was withdrawn from the market because of 60 deaths from rhabdomyolysis,¹⁷ more than 1,000 deaths with atorvastatin and rosuvastatin did not cause such concern, probably because they were labeled as acute kidney failure deaths.

Hepatitis includes hepatitis A, B, C, cholestatic, autoimmune, fulminating, acute, chronic and viral, including cytomegalovirus. All of these terms must be included in this compilation of damage reports. However, the overwhelming majority of these reports said simply “hepatitis” with no qualifier. Liver damage has always has been a concern with statin use.

I picked search terms that might give a measure of ALS occurrence because Ralph Edwards of the World Health Organization reported excessive numbers of peripheral neuropathy and atypical ALS cases associated with the use of atorvastatin worldwide, using the Vigibase data.¹⁸ In 2012 MedWatch began coding for ALS. In 2009 Joe Graedon started a People’s Pharmacy link and invited anyone developing symptoms suggestive of ALS (Lou Gehrig’s disease) while taking statins to comment on their status for the benefit of others.¹⁹ Graedon notes that FDA has dismissed the concerns.

The incidence of new diabetes in statin users is now considered to be close to 12%.²⁰ This is an amazing user penalty for a medicine that is supposed to diminish the risk of cardiovascular disease! I used the search term “pancreatitis” to see how much of this diabetes might reflect organ damage.

CoQ10 inhibition is felt to be a major contributor to heart failure in statin users.²¹ I searched for “myocardial infarction” out of curiosity about how many might there be in a group already on statins.

Other Statin Drugs

Note that the preceding information concerns only atorvastatin and rosuvastatin during the time period 2006–2013. We have not counted the ADRs associated with the use of pravastatin (Pravachol), lovastatin (Mevacor), simvastatin (Zocor), and fluvastatin (Lescol) in either their single or combined use.

Water-soluble statins like atorvastatin, simvastatin, and lovastatin should in theory have fewer cognitive ADRs compared with the fat-soluble statins like rosuvastatin and pravastatin because of less brain penetration.²² This effect, if it exists, is only relative because the cognitive ADR load seems to be shared by all statins, with atorvastatin getting the most blame because it is prescribed far more often.

Failure to Warn

Ubiquinone and dolichol inhibition are well known to the pharmaceutical industry, which has considered the idea of recommending supplemental CoQ10 (see above). Merck never used its patent for the combination of CoQ10 with statins in one prescribed dose, nor did it share its concerns on the matter with the medical community. Bliznakov has done an excellent review of this self-serving action by Merck,²³ with particular emphasis on the critical role of CoQ10 in body function.

This oversight by Merck laid the groundwork for Dr. Sidney Wolfe's Public Citizen petition²⁴ of Aug 20, 2001, and Dr. Julian Whitaker's May 23, 2002, petition to FDA.²⁵ Dr. Wolfe's petition called for special "black box" warnings to doctors and patients about the life-threatening muscle damage of statin drugs, calling attention to the fact that 81 people had died from statin-related rhabdomyolysis since the time the drugs were first marketed in 1987. Dr. Whitaker's petition called on the FDA commissioner to change the package insert on all statin drugs and to issue a "black box" warning to consumers of the need to take CoQ10¹⁴ whenever they take a statin drug. However, no action was taken on this petition. Of relevance here is the fact that in Canada the atorvastatin warning label is strengthened to include warnings not only about CoQ10 depletion but also about the closely related L-carnitine deficiency.

Problems related to these deficiencies can occur in any tissue: muscle, nerve, or brain. Thus, these concerns are relevant to patients experiencing signs of statin-associated myopathy, neuropathy, ALS-like condition, and even cognitive dysfunction.

The diminished bioavailability of intracellular CoQ10 and dolichols associated with the use of statins has the potential for seriously increasing oxidative damage and mitochondrial DNA mutations.²⁶ The anti-inflammatory benefits of statins are mediated by their special effect on the NF- κ B cellular transcriptases and aggravated by inhibition of such antioxidants as CoQ10.¹⁵ The logical consequence of this is premature aging and the progressive development of such chronic conditions of aging as muscle weakness, burning pain,

incoordination, and faulty memory—exactly the clinical picture we are seeing in tens of thousands of statin users.

Individual Variability

The clinical responses we are seeing from this process of progressive mitochondrial damage is highly variable, more of a spectrum than a predictable, precise display of symptoms. We first have to accept that most statin users appear to do quite well on statins. This suggests that in some people the mevalonate pathway must take several different forms, perhaps involving bypass channels, that allow sufficient CoQ10, dolichols, selenoproteins, etc., to be available despite blockade of the basic mevalonate pathway.

With the advent of increasingly sophisticated genetic screening, much has been learned in these past few years directly bearing on statin toxicity. It appears that some people are born with various genetic combinations that greatly increase sensitivity to the various statin drugs. These are related to the SLCO1B1 polymorphism,²⁷ which has significant effects on the pharmacokinetics of different statins. Its greatest effect was found to be on the plasma concentration of simvastatin. It also increased the plasma concentrations of atorvastatin, pravastatin, and rosuvastatin.

Large differences in frequency of these genetic combinations exist between different populations. The highest frequencies of these variant genotypes were found in America (mean 24%; range, 18–32%) with similar but slightly smaller figures for Europe (mean, 18%; range 14–23%). Thus, in the U.S., about 24% of our population is born with a super-sensitivity to statins, so that the usual dose gives blood levels far higher than expected.

We also find that some persons are completely unresponsive to statins, strongly supporting the presence of alternative pathways. In my 23 years of clinical medicine I soon discovered that doctors are fortunate if six out of every 10 patients have the expected response to a given medicine.

It is also possible that premature aging and the earliest forms of neuropathy and myopathy may not yet be clinically apparent. Dull aches, slight numbness, "senior moments," and personality change can be so subtle as to escape recognition, so at least some of those who appear to be tolerant may actually have subclinical decline in function.

I have generally categorized the symptoms as cognitive, emotional, neuropathic, myopathic, and neurodegenerative, but in reality there is much overlap. There is also generalized fatigue, the result of ATP lack. With sufficient mitochondrial DNA damage, fatigue becomes inevitable.²⁸

An individual can present with any one or all of these symptoms. It all depends upon what kind of body tissue is the most involved with mitochondrial deterioration. Every cell comes equipped with mitochondria, the energy producers of the cell.

The cells of slowly metabolizing tissue may contain only a few mitochondria because energy needs are minimal.

Muscle, heart, and brain cells come equipped with hundreds or thousands of mitochondria because of the urgency of their metabolic demand.

There is no way to predict how any one person will respond to this progressive mitochondrial deterioration triggered by statins. Therefore, a cognitively impaired victim may also present with emotional symptoms, painful neuropathy, disabling myopathy, an ALS-like manifestation, or with just cognitive dysfunction alone. It depends on individual vulnerability.

Physician Response

Many physicians have been committed for decades to the use of reductase inhibitors (statins). They are delighted to have a method to prevent a common and devastating cause of disability and death. After almost 40 years of treating hyperlipidemia with relatively ineffective medicines, there was finally had a drug that really worked. Cholesterol dropping 40 points in just a few weeks was a whole new world.

There was hardly a word about side effects. Friendly pharmaceutical representatives and direct-to-patient advertising advised a “simple blood test” after a few weeks to check liver function. A few muscle problems, in fewer than 2% of our patients, were anticipated, and the remedy was to drop the dose a bit.

Physicians do not like to admit to being wrong about their practice philosophy—and after all, they have been following their national leaders, and the supposedly “settled” science about the cholesterol causation of arterial damage.

FDA has a first-rate monitoring system, but it is grossly deficient for reporting findings back to the medical community. The average primary-care physician in our country today, even knowing that only a minority of patient problems get reported to FDA, would be startled to see the figures for cognitive dysfunction, neuropathy, rhabdomyolysis, depression, neuropathy, and hepatitis.

Responsible physicians must demand full information on drug adverse reactions.

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