**Statin Side effects**

<http://www.spacedoc.net/zocor_UK_side_effect_reports> **( Data Source)**

**Abstract**

**Objective:** What prompted me to do this personal search of what most would agree is FDA's business is the almost total lack of awareness in the medical community of the many cases of cognitive dysfunction, severe emotional and behavioral disorders and disabling neuro-muscular degeneration associated with the use of statin drugs. I knew that thousands of reports of these conditions had gone into Medwatch. What is wrong with　the ADR reporting system, I wondered, that　the medical community seems unaware of these reports of statin damage?

**Methods:** I gained access to a CD of actual Lipitor Medwatch data from the period Nov 1997 to early 2007. Using the usual PC search mechanism, it was technically straight-forward to count out numbers of case reports for each search term I entered.

**Results:** The numbers of case reports for such search terms as **severe cognitive dysfunction** (662), **neuropathy** (547**),　 rhabdomyolysis** (1592) , **depression** (517), **unusual weakness** (1158) and **hepatitis** (951) during the reporting period are particularly impressive to most MDs when weighed against their awareness that the true incidence of side effect reporting may be ten to one hundred times the reported incidence.

**Conclusions:** There is reason to suspect that because of unreliable FDA reporting of significant Medwatch data, the medical community has been grossly misled as to the true magnitude of the statin drug side effect problem.

 **INTRODUCTION**
If Medwatch is the protective health "umbrella" in the United States for post-marketing ADRs, how is it that eight years after the official Medwatch reporting of my personal Lipitor-associated transient global amnesias to FDA, the Chief of Cardiology of a major university/teaching hospital can tell me recently during a symposium that he had never heard of any significant cognitive problems from statin drugs? He was lecturing a large group of medical personnel about statin drug use. Similarly, it was Ralph Edwards of the World Health Organization's Vigibase drug monitoring system who announced to the world "excess ALS associated with statin use worldwide, " while FDA stood silent. They apparently had missed it. And why aren't doctors aware that over the past eight years some 20 rhabdomyopathy deaths per year are caused by Lipitor alone? It is for this reason that I suspected that Medwatch information on statin ADRs is not being adequately reported back to the doctors who write the prescriptions.I was the recipient of a CD from FDA containing all the Lipitor ADRs from November 1997 through January 2007.　 I manually counted case reports for each search term. Although special software exists to make this task less cumbersome it is available only to drug company and FDA personnel. One of the benefits of retirement is time to do the important things.

**RESULTS**

Based upon my personal experience with this drug (see Lipitor, Thief of Memory) "amnesia" was the first search term I entered. Not unexpectedly, 399 case reports resulted. The search term "memory impairment" produced another 263 cases. This total of 662 reports of serious cognitive dysfunction associated with the use of Lipitor seemed to fit quite well with the total numbers of such reports entered in my repository over this same time period. I was concerned only with the more severe forms of cognitive loss during this phase of my study and was not at this time looking for such conditions as confusion, forgetfulness, disorientation or aggravation of senility. Knowing of the hundreds of neuropathy cases in my repository and many of them associated with Lipitor, "neuropathy**"( the common causes of painful peripheral neuropathies are herpes zoster infection, HIV-related neuropathies, nutritional deficiencies, toxins, remote manifestations of malignancies, genetic, and immune mediated disorders.)** was the next search term I entered. I counted a total of 547 Lipitor "neuropathy" reports to Medwatch during this time period. I would not call this minor especially since this condition has proven to be very resistant to traditional treatment and many appear to be permanent. This is though in a climate resistant to the concept of statin associated neuropathy which encourages the more widespread use of statins in diabetics despite compelling research by Gaist **(1) and others that the risk of neuropathy from statin use is 16 times greater than from diabetes alone.** Next I used the search term "Guillain Barre syndrome"　 which produced　 42 reports for this unusual form of peripheral neuropathy. Prompted by the many hundreds of reports I have received where the major complaint of statin victims is leg and arm pain, I used the search term "pain in extremity", yielding 1799 reports. Then I used the search term "rhabdomyolysis" **( Rhabdomyolysis is the rapid breakdown (lysis) of skeletal muscle tissue (rhabdomyo) due to injury to muscle tissue. The muscle damage may be caused by physical (e.g. crush injury), chemical, or biological factors.).** This was the nemesis of Baycol, amassing nearly one hundred deaths before being removed from the market. Deaths from rhabdomyolysis are only a small part of the total number of hospitalizations. Still the number I counted of 1,592 jolted me. I knew there were still problems from this cause but somehow never expected that this number of hospitalizations would come from just this one statin drug. I referred to Sidney Wolfe's Table 1, done at the time he was trying to gain support for Baycol's removal from the market.

**Table 1:**
**Cases of Statin-Associated Rhabdomyolysis by Drug (October 1997 through December 2000)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 　**Drug** | **Number of Cases** | **% of Total Cases** | **Cases without Fibrates** | **Percentage of　cases without Fibrates** |
| 　Atorvastatin | 　86 | 11.1%　 | 73　 | 84.9%　 |
| 　Cerivastatin | 387 | 50.1% | 187 | 48.3% |
| Fluvastatin　 | 10 | 1.3% | 8 | 80.0% |
| Lovastatin　 | 32 | 4.1% | 30 | 93.8% |
| Pravastatin | 70 | 9.1% | 62 | 88.6% |
| Simvastatin | 187 | 24.2% | 164 | 87.7% |
| **TOTAL** | **772** | 　 | **524** | **67.9%** |

Even though cerivastatin ( Baycol ) was the big player in the rhabdomyolysis field back then, it is obvious that the contribution of cases from other statins was considerable. **Half of all** **rhabdomyolysis cases it seems were due to statins** other than Baycol, so all doctors expected to see more of this dreaded complication despite Baycol's withdrawal from the market. But still the number 1592 reported for Lipitor seemed excessive, particularly when a glance at Wolfe's　Table 2 shows us that approximately 10% of rhabdomyolysis cases result in death.

**Table 2.**
**Deaths reported in Statin-Associated Rhabdomyolysis ( October 1997 through December 2000)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **Number of　Cases** | **Percent of　 Total Deaths** | **Cases without Fibrates** | **Percent of cases of each drug without Fibrates** |
| 　Atorvastatin | 　13 | 18.1%　 | 　 11　 | 84.6% |
| 　Cerivastatin | 　20 | 　27.8% | 　10 | 　50.0% |
| 　Fluvastatin | 　1 | 　1.4% | 　1 | 　100% |
| 　Lovastatin | 　5 | 　6.9% | 　5 | 　100% |
| 　Pravastatin | 　9 | 12.5%　 | 　8 | 88.9%　 |
| 　Simvastatin | 　24 | 　33.3% | 　19 | 　79.2% |
| **Total** | **72\*** | 　 | **54\*\*** | **75%** |

Dr. Wolfe's table of statin rhabdomyolysis events by drug for the time period 10/1/03-9/30/04, Table 3, suggests that although Lipitor remains a major player, Crestor now shares center stage along with Zocor.

 **Table 3:
Comparative Rates of Rhabdomyolysis Reports to FDA**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 　**Drug** | **Rhabdomyolysis reports to FDA (10/1/03-9/30/04)** | **Rx's Filled (millions)(10/1/03-9/30/04)** | **Rhabdomyolysis reports per　million Rx's** | **Crestor rate as multiple of other rates** |
| 　Crestor | 　68 | 5.2　 | 13.1　 | --　 |
| 　Zocor | 　139 | 29.8　 | 4.7　 | 2.8　 |
| 　Mevacor | 　16 | 8.0　 | 2.0　 | 6.6　 |
| 　Lipitor | 　87 | 66.6　 | 1.3　 | 10.1　 |
| 　Lescol | 　2 | 2.1　 | 0.95　 | 13.8　 |
| 　Pravachol | 　9 | 15　 | 0.60　 | 21.8 |
| 　All statins 　except Crestor | 　253 | 121.5　 | 2.1　 | 6.2　 |

Adding all of the rhabdomyolysis reports for the 12 month period - 253 plus Crestor's 68 - produces the total of 321. Applying Wolfe's 10% figure to the 321 total cases for the year produces a possible 32 deaths from statin rhabdomyolysis for that 12 month period. The estimate, using Dr. Wolfe's formula,　 for the average number of Lipitor rhabdomyolysis deaths/year during the period I studied is 20. I next searched for words that might reflect the apparent **effects of statin drugs on emotion and behavior now being reported by statin users** and being actively researched by Dr Beatrice Golomb (2), Director of the statin study at UCSD college of Medicine. **Such reports range from suicides, to a homicide, to a an arrest for physical assault, and to extreme road rage type behavior**. I found 166 reports using search terms focusing on the "aggressiveness" (24), "hostility" (11), "anger" (30), "paranoia" (16) and "irritability" (85) commonly reported in statin users and 602 reports of "depression" (517) and "suicidal ideation" (85).　　My next search term was based upon the recent report from a French database concerning their experience **with statins and tendon complications,** finding 96 reports in the period 1990 to 2005. Medwatch Lipitor reports total 191 for a comparable time period. This relatively obscure finding is based upon the role of cholesterol in tendon and ligament function and is generally not recognized. The next search term was **"hepatitis**". Before I tell you the number, I first must qualify it by warning that there are many different kinds of hepatitis. There is hepatitis A, B, C, cholestatic, autoimmune, fulminating, acute, chronic and viral, including cytomegalovirus. All of these terms are used in this compilation of Lipitor damage reports. However, the overwhelming majority of these reports said simply, "hepatitis" with no qualifier. **Since hepatitis always has been a warned concern from statin use** you must make up your own mind in interpreting the 951 total cases that resulted. When I found that "liver function abnormalities" also was being used in the Medwatch diagnoses list, I used it as a search term, reporting 375 liver function abnormalities in addition to my 951 hepatitis cases. Since the unexpected association of ALS with statin use was reported recently by Ralph Edwards of the World Health Organization, using Vigibase data, my next investigation of Lipitor Medwatch data was for search terms that might give a measure of ALS occurrence. Using ALS or Lou Gehrig's disease drew a blank.　 **"Unusual weakness"** turned up 1158 case reports,　 "balance disorders" gave 248 responses, "nervous system disorders" gave 116, "coordination abnormalities" gave 72 responses and "asthenia", a symptom common to several neurodegenerative diseases, including ALS, gave 178 reports. Most MDs would tend to consider asthenia so close to muscle weakness in definition as to defy clinical separation so the unusual weakness category now becomes 1336 by the addition of the 178 for asthenia. As mentioned earlier, Medwatch reports are generally thought to be only 1-10% of true incidence. Applying this to the search term "unusual weakness" as an example, gives a possible range of 13,360 case reports (10% reported) to 133,600 case reports of this condition (1% reported.) The remainder of my informal survey included 318 reports of "pancreatitis" 99 reports of "dementia" 240 case reports of "disorientation" 249 reports of "confusional state" 69 reports of "arthralgia" 574 reports of "myalgia", 207 reports of "musculoskeletal stiffness" and 101 reports of "musculoskeletal pain." I also tried the search term "cardiac failure" and turned up 338 reports. Many of these may be associated with **statin induced CoQ10 inhibition** and as such are similar in etiology to the "asthenia" mentioned previously, both referencing energy lack. I chose my next search term "**myocardial infarction"( Myocardial infarction (MI or AMI for acute myocardial infarction), commonly known as a heart attack, occurs when the blood supply to part of the heart is interrupted)** purely out of curiosity as to how many might there be in a group already on Lipitor. The figure was 1258 - another attention getter - especially when I got 505 additional reports using the search term "coronary artery occlusion". I terminated the pure curiosity part of my Medwatch review efforts with the search term "cerebrovascular accident" with 720 reports to which another 5 were added by the search term "cerebral artery occlusion" and another 68 inferred by the use of the search term "aphasia."

**DISCUSSION**
It is generally understood that the simple association of a sign or symptom with the use of statins does not of itself imply causality. Only when the numbers of case reports become clearly excessive or specially unique in character is one justified in considering a possible cause and effect relationship.

**One is reminded here of the beginning of the misguided war on cholesterol** when elevated cholesterol was associated with proneness to atherosclerosis. Inferring cholesterol causation on the basis of association is roughly the same as saying the presence of firemen at fires clearly proves causal relationship. Nevertheless we did it with cholesterol and brainwashed two generations of doctors. In this study we do have numbers that for some of the conditions studied seem clearly excessive and the memory loss data is sufficiently unique by known statin mechanism of action to justify special concern. **Only in the year 2003 did Pfrieger (3) publish his evidence that cholesterol was critical to memory function.** He demonstrated that hippocampal synapses **for memory were completely dependant upon abundant cholesterol and revealed to the world that glial cells are charged with this function in humans**. Circulating blood cholesterol is not available to the brain, Pfrieger tells us, because the lipoprotein/cholesterol molecule is far too large a molecule to cross our blood brain barrier. Memory function is completely dependant upon glial cell synthesis of cholesterol and naturally glial cells were just as sensitive to statin effect as any other cell in our body. **When glial cell synthesis in impaired, cholesterol falls and with it memory function.** Whereas some **respond with transient global amnesia, others respond with short-term memory loss, confusion, disorientation and increased forgetfulness**. Although some will state, "I have been on statins five years with no memory problems" Muldoon (4) has shown on two occasions, once with Mevacor and again several years later with Zocor, **that 100% of statin users show cognitive loss if sufficiently sensitive testing is done**. From the very beginning statin makers have told us that statins are reductase inhibitors **(A substance that blocks an enzyme needed by the body to make cholesterol and lowers the amount of cholesterol in the blood. HMG-CoA reductase inhibitor drugs are called statins. Also called hydroxymethylglutaryl-coenzyme A reductase inhibitor.)** but they never old us what that really meant. Most doctors had complete faith in the pharmaceutical industry to do the right thing so they never bothered to look up reductase inhibition in their dusty biochemistry books. If they had, they would have found this reductase step is at the very beginning of the mevalonate pathway, a collection of biochemical steps critical not only for cholesterol synthesis but also for CoQ10 and dolichol and selenoprotein synthesis, Rho activation and normal phosphorylation. **When statins block cholesterol synthesis all of these other functions are blocked to the same degree**. It is like girding a tree. You do not cut just cholesterol synthesis with statins; you inevitably cut all other mevalonate functions (**is a key organic compound in biochemistry. It is a precursor in the biosynthetic pathway, known as the HMG-CoA reductase pathway, that produces terpenes and steroids**). In their priority for cholesterol reduction, the drug companies led us to complete acceptance of these inevitable effects on these other elements of the pathway as collateral damage. These drugs were marketed to a nation of guinea pigs, for none of this possible harm had been researched at all and so the statin drug side effects began to accumulate. Cognitive side effects, we soon learned, were due to glial cell inhibition by statins and failure of Rho activation (5).　 Problems with cell wall integrity loss, interference with energy formation and increased mitochondrial mutations all relate to CoQ10 interference.

Dolichol inhibition led to problems with glycoprotein synthesis critical for neuropeptide synthesis, cell identification, cell messaging and immunodefense. No longer could we identify DNA errors and correct them, for glycoproteins are involved, aiding and abetting the DNA mutation rate. The list goes on and on. And now over the past decade there have been thousands of victims with cognitive deficits, permanent neuropathies and myopathies, chronic neuromuscular degeneration and chronic neurodegenerative disease such as ALS and Parkinsonism. All of these conditions have been associated with the use of statins yet causality has been all but impossible to prove. Recently, however, evidence has been mounting that just might change all this for the ultimate effect of mevalonate blockade of CoQ10 and dolichols is mitochondrial mutations, inducing structural changes that can be visualized.　　Now we find that among the many side effects of statin drug use is the same **direct assault on mitochondrial DNA and the energy equation produced by natural aging. The well-known statin side effect of coenzyme Q10 inhibition bears directly upon the effectiveness of the anti-oxidation system, leading directly to excess ROS (reactive oxygen species) production with its age-like mutagenic consequences. SERIOUS DAMAGE!!!** Additionally, another well-known statin side effect, that of dolichol inhibition, results directly in failure of glycoprotein synthesis and loss of effectiveness of many of our glycoprotein based systems, such as glycohydrolases **for detection and correction of DNA damage**. Statin drugs cause effects on our mitochondria identical to those that accumulate with age. **One might say that one side effect of statin therapy is premature aging.** Now I believe I know why many statin side effects are permanent and why weakness and fatigue are such common complaints. Many statin victims say that abruptly, almost in the blink of an eye, they have become old people. MD's, for the most part unaware of the truth because FDA has not informed them, reassuringly say, "You have to expect these things now. You are not fifty any more." Unwittingly our doctors have come close to the mark, **for aging is what statins appear to do.** During the past two decades much has been learned about mitochondrial myopathies and their association not only with ragged red myofibrils but also with a great variety of neuro-degenerative syndromes. In 1995, Rifai, Z and others (6) after studying the frequency of ragged red fibers in muscle biopsy specimens, reported in Neurology that that the number of ragged red fibers increases with **normal aging and may reflect an age-related decline in muscle mitochondrial oxidative metabolism.** What was known then as inclusion body myositis consistently revealed ragged red myofibrils marking it as secondary to a defect in the respiratory chain and therefore metabolic in origin rather than inflammatory.
During this time period muscle CoQ10 was found to be deficient in these metabolic myopathy cases. This is clearly, to me, associated with the known inhibitory effect of statins on mevalonate derived CoQ10. **Although CoQ10 plays a primary role in the energy equation of the body it is also a powerful anti-oxidant that along with glutathione helps to prevent excess buildup of free radicals. In the event of lack of availability of sufficient CoQ10 and glutathione, more rapid mitochondrial mutations result**. The normal mutation **rate for mitochondria is some 4-8 times that of somatic cells so the effect of CoQ10 lack can be severely mutagenic**. In 2003 Carvalho and others (7) reported eight cases of statin associated myopathy associated with histologic changes very similar to these earlier metabolic myopathy cases, including muscle biopsy evidence of ragged red myofibrils. Some had elevated CK enzymes; many did not. There followed a host of reports of unusual statin associated myopathies associated with a large variety of brain and other organ defects.　 Now we find that these pioneering studies of metabolic myopathies have led us to "ragged red fibers" the marker we have been looking for. The number of ragged red fibers in a muscle biopsy will correlate not only with age but also degree of statin associated decline in muscle mitochondrial oxidative metabolism. **This is the consequence of statin associated inhibition of CoQ10 and dolichols.** 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 the United States, knowing that perhaps only 10% of patient problems get reported to FDA, would be startled to see these figures, especially the ones for cognitive dysfunction, neuropathy, rhabdomyolysis, depression, neuropathy and hepatitis. These are the people who write the prescriptions for statin use.

**CONCLUSIONS**
Although abundant research evidence now supports the reality of serious statin damage in susceptibles, primarily the consequence of mevalonate inhibition by statins, most of the medical community appears unaware of this. A major　 contributing factor has been lack of meaningful feedback of Medwatch data back to the doctors.

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**Zocor® ( Simvastatin ) - UK Side Effect Reports**

In the United Kingdom there exists an organization devoted to studying adverse drug reports (ADRs). This counterpart to the U.S. FDA ( Food and Drug Administration ) is the MHRA ( Medicines and Healthcare products Regulatory Agency.) However, there is a major difference in the way they operate. The MHRA organization actually studies the data, organizes it and makes it available to their medical community. A friend of mine in England recently sent their report of Zocor ADRs to me as an information item. I consider it to be one of the most astonishing documents to come out of the statin era. I must assume that UK physicians take advantage of this. How else can they select treatment options? Physicians in the United States are, with few exceptions, largely unaware of these statin drug side effect realities.

**Drug Analysis Print (MHRA, UK)**
**Drug name: SIMVASTATIN**
**Period covered:** From first marketing of Zocor ( Simvastatin ) in the UK in the early 1990s to 21-Nov-2008

|  |  |  |
| --- | --- | --- |
| **Reported Problem from Simvastatin** | **All** | **Fatal** |
| Blood disorders　　 | 82　 | 　1 |
| Cardiac disorders  | 172 | 　10 |
| Congenital disorders | 11 | 　0 |
| Ear disorders | 56 | 　0 |
| Endocrine disorders　 | 14 | 　0 |
| Eye disorders　 | 233 | 　0 |
| Gastrointestinal disorders　 | 1167 | 　4 |
| General disorders　　 | 1004 | 　13 |
| Hepatic disorders | 16 | 　2 |
| Immune system disorders | 31 | 　0 |
| Infections　 | 70 | 　6 |
| Injuries　 | 75 | 　0 |
| Investigations　 | 696 | 　0 |
| Metabolic disorders | 141 | 　0 |
| Muscle & tissue disorders　 | 2058 | 　12 |
| Neoplasms　　 | 41 | 　5 |
| Nervous system disorders | 1267 | 　2 |
| Pregnancy conditions　 | 16 | 　2 |
| Psychiatric disorders　　　 | 749 | 　2 |
| Renal & urinary disorders　　　 | 218 | 　3 |
| Reproductive & breast disorders　　　　 | 187 | 　0 |
| Respiratory disorders　　　　 | 324 | 　4 |
| Skin disorders　 | 1107 | 　0 |
| Social circumstances　　  | 7 | 　0 |
| Surgical & medical procedures　　　  | 2 | 　0 |
| Vascular disorders　　 | 111 | 　0 |
| **TOTAL NUMBER OF REPORTED REACTIONS** | **10055**  | **66**　　　　　 |

For comparison, my report of US FDA ADRs for Lipitor can be found here