

Frequently Asked Questions (FAQ) about Statin Adverse Effects

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Updated 13 March 2005:

Frequently Asked Questions about Statin Adverse Effects

Introduction

Statin adverse effects include muscle damage, nerve damage, cognitive damage, memory loss, amnesia, chronic pain, chronic fatigue, and many other problems. Some, like rhabdomyolysis, kidney and liver damage, can be fatal. Others can cause serious disability. Statin users and their families should be aware of the possible adverse effects, so that they can detect them early and discuss them with their doctors.

This FAQ includes references to studies published in medical journals that may help the physician better understand statin adverse effects.

If adverse effects are detected, the patient should request that the doctor report them to the FDA and the NIH-funded Statin Study. This request to the doctor can be made in writing, similar to the example below:

To my physician,

I believe that my symptoms may be due to the adverse effects associated with cholesterol-lowering statin drugs. I need your help to understand the cause of my symptoms, treatment options, and the prognosis for my recovery.

Please review the references below, published medical studies that show similar problems associated with statin drugs. These are made available via the National Institutes of Health (NIH, <http://www.ncbi.nlm.nih.gov/Entrez/>) library of biomedical journal citations and other major repositories of medical research.

Also, I am respectfully requesting that you file an adverse effects report with the FDA (<http://www.fda.gov/medwatch/how.htm>), and that you please send a copy of the report to the to the NIH-funded Statin Study, attention: Dr. Beatrice Golomb, Principal Investigator.

Statin Study website: <http://medicine.ucsd.edu/statin/>

Statin Study contact info: <http://medicine.ucsd.edu/statin/contactinfo.html>

UCSD STATIN STUDY E-MAIL ADDRESS: statinstudy@ucsd.edu

MAILING ADDRESS: UCSD Statin Study 9500 Gilman Dr. La Jolla, CA 92093-0995

PHONE NUMBER: (858) 558-4950

In Canada:

Health Canada:

http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_adverse_report_e.html

PharmaWatch:

<http://www.pharmawatch.net/>

Thank you

What are the names of the Statin drugs?

The Cholesterol-lowering Statin Drug Names: Lipitor, Crestor, Mevacor, Pravachol, Zocor, Lescol, and Baycol, aka atorvastatin, rosuvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin; This class of drugs is also known as HMG-CoA Reductase Inhibitors, short for 3-Hydroxy-3-Methyl-Glutaryl Coenzyme A Reductase.

[http://www.bms.com/cgi-](http://www.bms.com/cgi-bin/anybin.pl?sql=select%20PPI%0A%09%09%09%09%20%20%20from%20TB_PRODUCT_PPI%20%0A%09%09%09%09%20%20%20where%20PPI_SEQ%20=%2056&key=PPI)

[bin/anybin.pl?sql=select%20PPI%0A%09%09%09%09%20%20%20from%20TB_PRODUCT_PPI%20%0A%09%09%09%09%20%20%20where%20PPI_SEQ%20=%2056&key=PPI](http://www.bms.com/cgi-bin/anybin.pl?sql=select%20PPI%0A%09%09%09%09%20%20%20from%20TB_PRODUCT_PPI%20%0A%09%09%09%09%20%20%20where%20PPI_SEQ%20=%2056&key=PPI)

http://www.ca.pharma.novartis.com/downloads/e/lescol_scrip_e.pdf

http://www.merck.com/product/usa/pi_circulars/m/mevacor/mevacor_pi.pdf

http://www.merck.com/product/usa/pi_circulars/z/zocor/zocor_pi.pdf

What is the “Statin Study”?

Dr. Beatrice Golomb is doing research for the National Institutes of Health (NIH) into “non-cardiac endpoints” of the statin drugs. In other words, what do statins do besides reducing serum cholesterol? The UCSD Statin Study is conducted at the University of California, San Diego, and it accepts NO INDUSTRY FUNDING. You can, and should, contact the Statin Study with information on any adverse effects. It is to everyone’s benefit that the UCSD Statin Study has the most complete set of information on statin adverse effects in the world. You can email, write, or call:

statinstudy@ucsd.edu

UCSD Statin Study

9500 Gilman Dr.

La Jolla, CA 92093-0995

(858) 558-4950

More information at the website: <http://medicine.ucsd.edu/statin/index.htm>

Where can I look to find information on research studies of statin drugs?

The National Institutes of Health has a website, <http://www.ncbi.nlm.nih.gov/Entrez/> that offers a search engine that is useful in finding the latest studies that have been published in medical journals (over 11,000,000 biomedical journal citations) and other major repositories of medical research. Each study usually comes with an Abstract, or summary of the findings. In most cases, should you want to see the full text of the study, the full article can be purchased online for approximately \$25 to \$40, depending on the journal, which is much cheaper than a subscription.

Note that journals publish new studies every month, so revisit the site often. Also, if you find a study that is pertinent to what you are looking for, check the links to the right that will take you to similar studies on the same topic. Finally, if you don't get a 'hit' on what you are looking for, try medical terminology synonyms. Search results are different when using different search terms. So, for example: "statin" or "atorvastatin" or "lipitor" or "reductase inhibitor" or "HMG-CoA". Similarly, "cholesterol" will return different results from "Dyslipidemia."

Why does my physician have such a difficult time believing that my physical problems might be an adverse effect of Lipitor or one of the other statins?

Statins are now the most widely prescribed of all prescription drugs, making them very big business. The Wall Street Journal Online, in a June 13, 2003 article, "As Drug Sales Teams Multiply, Doctors Start to Tune them Out; 'Arms Race' by Pfizer and Rivals Boosts Pill Prices, Ire, but No One Dares Retreat", reported that Pfizer's sales of Lipitor alone were \$8 BILLION for the year 2002. That is just for Lipitor alone, one of FIVE statins on the market today. The article states that in 2002 the drug companies spent over \$12 Billion on their sales forces. According to the article, "Last year, a few Pfizer reps brought along a guest speaker who was both a doctor and lawyer to a lunch meeting with doctors at Clinical Associates, a group practice in suburban Baltimore. He said they risked being sued if their patients didn't reach their cholesterol goals". Doctors are the ones who are primarily targeted by the advertising blitz to make the expectations of increased sales come true. In addition, consumers are marketed with slick commercials and ads. Doctors are very busy, and they are inundated with positive statin spin. They may think that, since everyone is taking it, if there were problems they would have heard about it. They may not take the time to dig out negative information, and there are no major sponsors to fund equal time for negative reports.

Only last year, in 2002, did the Journal of the American Medical Association begin annotating publications with the author's ties to the company studied, citing potential conflict of interest.

The British Journal of Medicine in their May 31, 2003 issue on the theme "Time to untangle doctors from drug companies", ran no less than 6 articles saying that too many of the published drug studies are no more than industry-sponsored infomercials, and cited the selective reporting bias whereby only pro-industry studies are published. These articles were entitled: "Research sponsored by drug companies is biased"; "Drug representatives may increase unnecessary GP prescribing"; "Reporting of clinical trials of drugs shows bias"; "Characteristics of General Practitioners who Frequently see Drug Industry Representatives: National Cross-Sectional Study"; "No more free lunches; Patients will benefit from doctors and drug companies disentangling"; "Information from drug companies and opinion leaders; Double standards in information for medical journals and practitioners should go" <http://bmj.com/content/vol326/issue7400/>

The Canadian CBC News ran a series of consumer articles on March 25, 2003, on the prevalent problem of medical ghostwriting. In this scheme, drug companies write a study favorable to their product and then "reward" a doctor who prescribes the drug by listing his name as the "author" in the publication.
<http://www.cbc.ca/consumers/market/files/health/ghostwriting/links.html>

Your physician should look into your physical adverse effects, regardless of suspected cause. Do not permit your physician to put you off when you express a concern. Too many people are reporting long-term, perhaps permanent, damage when statin therapy is continued despite the appearance of adverse effects. With rhabdomyolysis, death can result. With other side effects, disability can result.

Oddly, people consistently report doctors who are dubious of reported problems being due to statins, even when the problem is listed by the manufacturer on the Physicians' Information page for the drug. It may help, if you identify your problems with the findings of a published study, to print out a copy and bring it with you to the doctor's appointment. In some cases, the doctor may simply be terrified of a malpractice charge.

That is one of the purposes for this FAQ – to give people an additional tool to help them to communicate with their doctors.

Note: These articles documenting or speculating on adverse effects of statins are in the vast minority. Hundreds, even thousands, of articles and research have praised statins. Certainly the people with side effects are in the minority, and the benefits are fantastic. Still, the doctors who do attempt to publish about problems associated with statins are often very bitter: they feel they are up against a tremendous political bias and going against an incredibly powerful industry. Med Journal editors tend to insist that all negative findings be couched in terms of how, overall, the statins are doing tremendous good, and the major studies finding problems with statins have been the subject of a pro-statin editorial in the same journal. Further, the popular press is extremely reluctant to

cover negative research findings for the companies who are among their heaviest advertisers.

OK, I understand the doctor's need to read clinical study results, but where can I find out what other people are experiencing in plain language, and maybe share my experiences?

Yahoo Groups has a "Stopped_Our_Statins" group:

http://health.groups.yahoo.com/group/Stopped_Our_Statins/messages

The International Network of Cholesterol Skeptics is a doctors' discussion group that is open for viewing at:

<http://www.thincs.org/>

The Dispace statin boards were an excellent source, but were damaged by internet vandalism, and may or may not return. The URLs were:

Lipitor: <http://forum.ditonline.com/viewboard.php?BoardID=38>

Zocor: <http://forum.ditonline.com/viewboard.php?BoardID=41>

Lescol: <http://forum.ditonline.com/viewboard.php?BoardID=37>

Pravachol: <http://forum.ditonline.com/viewboard.php?BoardID=40>

Mevacor: <http://forum.ditonline.com/viewboard.php?BoardID=39>

AARP ran an article on statin drugs and asked for responses, these posts start at:

<http://community.aarp.org/n/mb/message.asp?webtag=rp-health&msg=743.1>

(at the bottom of the page, you can click to the next post)

Another board:

<http://www.rxlist.com/rxboard/lipitor.pl>

<http://www.rxlist.com/rxboard/lescol.pl>

<http://www.rxlist.com/rxboard/mevacor.pl>

<http://www.rxlist.com/rxboard/pravachol.pl>

<http://www.rxlist.com/rxboard/zocor.pl>

WebMD has a roundtable on Cholesterol:

http://boards.webmd.com/roundtable_topic/1121

Also, there is a newsgroup (access via your email program):

sci.med.cardiology

Are there any books on the topic?

Dr. Graveline, retired family MD, USAF Flight Surgeon, researcher in space medicine and US Astronaut, who suffered adverse effects from Lipitor, maintains several websites

and has written an excellent book about statin-related memory loss and amnesia, “Lipitor, Thief of Memory”, available through Amazon.com and elsewhere, with more info available at:

www.spacedoc.net (you can start here and read about his life and his books)

http://www.spacedoc.net/lipitor_thief_of_memory.html

<http://www.spacedoc.net/lipitor.htm>

http://www.spacedoc.net/statin_dialogues.htm

As of mid-January, 2005, you can buy Dr. Graveline’s second statin book, “Statin Drugs - Side Effects and the Misguided War on Cholesterol.”

See:

http://www.spacedoc.net/statin_side_effects.html

What are the Lipitor warnings and side-effects listed by the manufacturer on the physicians’ information?

For a full introduction to the list, view <http://www.lipitor.com/pi/default.asp> . Summary of some of the items on the website includes Warnings of liver dysfunction, and skeletal muscle rhabdomyolysis for the physicians information updated as of July 2004.

What are the Lipitor Adverse Events in Placebo-Controlled Studies listed by Pfizer in the Physician’s information?

For a full introduction to the list, view <http://www.lipitor.com/pi/default.asp>, the information below is from the version updated as of April 2002:

Body as a whole: Infection, Headache, Accidental Injury, Flu Syndrome, Abdominal Pain, Back Pain, Allergic Reaction, Asthenia;

Digestive system: Constipation, Diarrhea, Dyspepsia, Flatulence;

Respiratory system: Sinusitis, Pharyngitis;

Skin and Appendages: Rash;

Musculoskeletal system: Arthralgia, Myalgia.

What are the Lipitor Averse Events reported in patients treated with Lipitor in clinical trials listed by Pfizer in the Physician’s information?

For a full introduction to the list, view <http://www.lipitor.com/pi/default.asp>, the information below is from the version updated as of April 2002:

Body as a Whole: Chest pain, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.

Digestive System: Nausea, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer,

dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory System: Bronchitis, rhinitis, pneumonia, dyspnea, asthma, epistaxis.

Nervous System: Insomnia, dizziness, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia.

Musculoskeletal System: Arthritis, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis.

Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

Urogenital System: Urinary tract infection, urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special Senses: Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.

Metabolic and Nutritional Disorders: Peripheral edema, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.

Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

What are the Lipitor Adverse events associated with Lipitor therapy reported since market introduction, that are not listed above, listed by Pfizer in the Physician's information?

For a full introduction to the list, view <http://www.lipitor.com/pi/default.asp> It includes the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis.

REPORTING ADVERSE EFFECTS FROM STATINS

Where should I report adverse effects from statins?

Report to the FDA

<http://www.fda.gov/medwatch/how.htm>

Report to the Statin Study

Also, it is important to report side-effects to the Statin Study, funded by the National Institutes of Health and conducted at the University of California, San Diego.

Statin Study website: <http://medicine.ucsd.edu/statin/>
with contact info at:

<http://medicine.ucsd.edu/statin/contactinfo.html>

UCSD STATIN STUDY E-MAIL ADDRESS: statinstudy@ucsd.edu

MAILING ADDRESS: UCSD Statin Study 9500 Gilman Dr. La Jolla, CA 92093-0995

PHONE NUMBER: (858 558-4950)

Dr. Golomb, the principal investigator of the Statin Study, is an incredibly intelligent and active woman. Take a look at her Curriculum Vitae at:

<http://www.medicine.ucsd.edu/faculty/golomb/>

OK, what should I take to my doctor?

The citations below are grouped by different categories of damage. You can take the entire list, but it may be better to select those areas that describe the adverse effects you are concerned with. You would do well, however, to look at all of them, as people frequently have other concerns they thought were unrelated until viewing the list of adverse effects.

NERVE DAMAGE & STATINS

Frequently Asked Question: What medical research studies have been done on Statins and Nerve Damage that I can bring to my doctor's attention?

Golomb BA, Yang E, Denenberg J, Criqui M (2003),
Statin-associated adverse events. P95. Presented at the 43rd Annual Conference on Cardiovascular Disease Epidemiology and Prevention. Miami; March 5-8.

Chong PH, Boskovich A, Stevkovic N, Bartt RE.

Statin-associated peripheral neuropathy: review of the literature.

Pharmacotherapy. 2004 Sep;24(9):1194-203. Review.

PMID: 15460180 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15460180

“Based on epidemiologic studies as well as case reports, a risk of peripheral neuropathy associated with statin use may exist; however, the risk appears to be minimal. On the other hand, the benefits of statins are firmly established. These findings should alert prescribers to a potential risk of peripheral neuropathy in patients receiving any of the statins; that is, statins should be considered the cause of peripheral neuropathy when other etiologies have been excluded.”

Rajabally YA, Varakantam V, Abbott RJ.

Disorder resembling Guillain-Barre syndrome on initiation of statin therapy.

Muscle Nerve. 2004 Nov;30(5):663-6.

PMID: 15389662 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15389662

“We report a disorder resembling Guillain-Barre syndrome, occurring on initiation of simvastatin, in a 58-year-old man, who had experienced a similar but milder episode after starting pravastatin 6 months earlier. This case suggests that acute polyradiculoneuropathy may represent a rare but serious side-effect of statin treatment. It also raises the issue of the pathophysiology of acute neuropathy on statin exposure, with a hypersensitivity reaction resulting in an immune-mediated process being possible instead of the hypothesized mitochondrial dysfunction in chronic cases.”

Scola RH, Trentin AP, Germiniani FM, Piovesan EJ, Werneck LC.

Simvastatin-induced mononeuropathy multiplex: case report.

Arq Neuropsiquiatr. 2004 Jun;62(2B):540-2. Epub 2004 Jul 20.

PMID: 15273860 [PubMed - in process]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15273860

“The association between the use of statins and neuromuscular disease is currently being intensely discussed. We relate a 63 years old man with possible case of statin-induced neuropathy in a patient with dislipidemia in use of simvastatina at high doses. The electrophysiologic studies disclosed findings compatible with mononeuropathy multiplex, suggested by clinical prescutation of asymmetrical numbness and weakness. More common causes of mononeuropathy multiplex were excluded and the patient improved after the discontinuation of the drug.”

Statins and risk of polyneuropathy, A case-control study

D. Gaist, MD, PhD; U. Jeppesen, MD, PhD; M. Andersen, MD, PhD; L.A. García Rodríguez, MD, MSc;

J. Hallas, MD, PhD; and S.H. Sindrup, MD, PhD

<http://213.4.18.135/87.pdf> full text

From the abstract: “The authors verified a diagnosis of idiopathic polyneuropathy in 166 cases. The cases were classified as definite (35), probable (54), or possible (77). The odds ratio linking idiopathic polyneuropathy with statin use was 3.7 (95% CI 1.8 to 7.6) for all cases and 14.2 (5.3 to 38.0) for definite cases. The corresponding odds ratios in current users were 4.6 (2.1 to 10.0) for all cases and 16.1 (5.7 to 45.4) for definite cases. For patients treated with statins for 2 or more years the odds ratio of definite idiopathic polyneuropathy was 26.4 (7.8 to 45.4). CONCLUSIONS: Long-term exposure to statins may substantially increase the risk of polyneuropathy.”

Are users of lipid-lowering drugs at increased risk of peripheral neuropathy?

David Gaist, Luis Alberto García Rodríguez • Consuelo Huerta • Jesper Hallas • Søren H. Sindrup

<http://213.4.18.135/75.pdf> full text

<http://213.4.18.135/76.2.pdf> full text
<http://213.4.18.135/87.pdf> full text text

Pharmacodynamics: Statins and peripheral neuropathy

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(2) Department of Clinical Pharmacology Odense University, Odense, Denmark

Received: 6 July 1998 / Accepted in revised form: 1 October 1998

Abstract Volume 54 Issue 11 (1999) pp 835-838

<http://link.springer-ny.com/link/service/journals/00228/bibs/9054011/90540835.htm>

Association of HMG-CoA reductase inhibitors with neuropathy.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12549960&dopt=Abstract

Ann Pharmacother. 2003 Feb;37(2):274-8.

Backes JM, Howard PA.

Department of Pharmacy Practice and Lipid, Atherosclerosis, Metabolic and LDL-Apheresis Clinic, University of Kansas Medical Center, Kansas City, KS 66160-7231, USA. jbackes@kumc.edu

“Epidemiologic studies and case reports suggest an increased risk of peripheral neuropathy with statin drugs... The majority of cases were at least partially reversible with drug cessation.” (emphasis added)

Moosmann B, Behl C.

Selenoprotein synthesis and side-effects of statins.

Lancet. 2004 Mar 13;363(9412):892-4. Review.

PMID: 15031036 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15031036

“We noted that the pattern of side-effects associated with statins resembles the pathology of selenium deficiency, and postulated that the mechanism lay in a well established, but often overlooked, biochemical pathway--the isopentenylolation of selenocysteine-tRNA([Ser]Sec). A negative effect of statins on selenoprotein synthesis does seem to explain many of the enigmatic effects and side-effects of statins, in particular, statin-induced myopathy.”

Statin therapy and small fibre neuropathy: a serial electrophysiological study.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12639733&dopt=Abstract

Lo YL, Leoh TH, Loh LM, Tan CE.

J Neurol Sci. 2003 Apr 15;208(1-2):105-8.

Department of Neurology, Singapore General Hospital, Outram Road, Singapore.

gnrlyl@sgh.com.sg

Describes 3 patients who developed neuropathy after ONE MONTH of statin therapy. “One patient redeveloped small and large fibre neuropathy when the similar drug was readministered.”

Peripheral Neuropathy and Lipid-Lowering Therapy

Paul E. Ziajka, MD, PhD, and Tammy Wehmeier, RN, Orlando, Fla.

Abstract: We report a case of peripheral neuropathy induced and exacerbated by several commonly used HMG-CoA reductase inhibitors including lovastatin, simvastatin, pravastatin, and atorvastatin, and the vitamin niacin. A review of the literature shows similar cases with individual lipid-lowering drugs, but this case shows the cross-reactivity of the neuropathic process to different HMG-CoA reductase inhibitors, and is the first reported case of a peripheral neuropathy exacerbated by the use of niacin.

<http://www.sma.org/smj1998/julysmj98/ziajka.pdf>

Phan T, McLeod JG, Pollard JD, Peiris O, Rohan A, Halpern JP.

Peripheral neuropathy associated with simvastatin.

J Neurol Neurosurg Psychiatry. 1995 May;58(5):625-8.

PMID: 7745415 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7745415&dopt=Abstract

Ahmad S.

Lovastatin and peripheral neuropathy.

Am Heart J. 1995 Dec;130(6):1321. No abstract available.

PMID: 7484806 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7484806&dopt=Abstract

Jacobs MB.

HMG-CoA reductase inhibitor therapy and peripheral neuropathy.

Ann Intern Med. 1994 Jun 1;120(11):970. No abstract available.

PMID: 8172444 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8172444&dopt=Abstract

Medication-induced peripheral neuropathy.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12507417&dopt=Abstract

Curr Neurol Neurosci Rep. 2003 Jan;3(1):86-92. Review.

Weimer LH.

Neurological Institute of New York, 710 West 168th Street, Unit 55, New York, NY 10032, USA. Lhw1@columbia.edu

PMID: 12507417 [PubMed - indexed for MEDLINE]

“Although most cases demonstrate acute or subacute onset after exposure, recent experiences with statin drugs raise the possibility of occult toxic causes of chronic idiopathic neuropathy.”

Le Quesne PM. Neuropathy due to drugs. In: Dyck PJ, Thomas PK, Griffin JW, et al, eds. Peripheral neuropathy. 3rd ed. Philadelphia: Saunders, 1993:1571–1581.
(Book, no link)

Of interest:

MacDonald BK, Cockerell OC, Sander WAS, Shorvon SD (2000) **The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. Brain**

123:665-676

General background medical Info from

Related, but also will appear in other FAQs:

Neuromuscular Disease Center

Washington University School of Medicine, St. Louis, MO

Home: <http://www.neuro.wustl.edu/neuromuscular/index.html>

Under Disorders & Syndromes:

Select:

Myopathy: <http://www.neuro.wustl.edu/neuromuscular/maltbrain.html>

Neuropathy: <http://www.neuro.wustl.edu/neuromuscular/naltbrain.html>

Neuromuscular: <http://www.neuro.wustl.edu/neuromuscular/syaltbrain.html>

CNS (Central Nervous System):

<http://www.neuro.wustl.edu/neuromuscular/syaltbrain.html#cns>

Specifics,

MYOGLOBINURIA – RHABDOMYOLYSIS

<http://www.neuro.wustl.edu/neuromuscular/msys/myoglob.html>

Then see **Lipid Lowering Agent Myopathies**

<http://www.neuro.wustl.edu/neuromuscular/msys/myoglob.html#lipid>

Note that this connects to **CARDIAC + MYOPATHY**

<http://www.neuro.wustl.edu/neuromuscular/msys/cardiac.html>

And to **TOXIC NEUROPATHIES:**

<http://www.neuro.wustl.edu/neuromuscular/nother/toxic.htm#statin>

OR Locally supplied Search on “Statin” leads to:

TOXIC MYOPATHIES

<http://www.neuro.wustl.edu/neuromuscular/mother/myotox.htm>

Note also tht under **Mitochondrial Disorders**, the list of problems associated with **Coenzyme Q10 Deficiency**

<http://www.neuro.wustl.edu/neuromuscular/msys/myoglob.html#coq10>

MITOCHONDRIAL MYOPATHIES

Facts About Mitochondrial Myopathies from the Muscular Dystrophy Association

MEMORY LOSS & STATINS

Frequently Asked Question: What medical research studies have been done on Statins and Memory Loss, or other mental problems that I can bring to my doctor's attention?

(Statins: Lipitor, Mevacor, Pravachol, Zocor, Lescol, and Baycol, aka atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin; Nerve Damage: Neuropathy, peripheral neuropathy, polyneuropathy; See separate FAQ for memory loss, cognitive damage, amnesia and aphasia, i.e., central nervous system (CNS) damage)

Am J Med. 2004 Dec 1;117(11):823-9.

Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults.

Muldoon MF, Ryan CM, Sereika SM, Flory JD, Manuck SB.

Center for Clinical Pharmacology, University of Pittsburgh, Pennsylvania 15260, USA.
mfm10@pitt.edu

“This study provides partial support for minor decrements in cognitive functioning with statins. Whether such effects have any long-term sequelae or occur with other cholesterol-lowering interventions is not known.” This is the second of two studies by Muldoon, both showing measurable cognitive decline in statin groups after only 6 months, using Neuropsych testing. Further, the cognitive deficits appear consistently in specific areas.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15589485

Golomb BA, Yang E, Denenberg J, Criqui M (2003),

Statin-associated adverse events. P95. Presented at the 43rd Annual Conference on Cardiovascular Disease Epidemiology and Prevention. Miami; March 5-8.

Muldoon MF, Ryan CM, Flory JD, Manuck SB (2002),

Effects of simvastatin on cognitive functioning.

Presented at the American Heart Association Scientific Sessions. Chicago; Nov. 17-20.

Muldoon MF, Barger SD, Ryan CM, Flory JD, Lehoczky JP, Matthews KA, Manuck SB.

Effects of lovastatin on cognitive function and psychological well-being.

After 6 months, 100% of the patients on placebos showed a measurable increase in cognitive function, and 100% of the statin patients showed a measurable decrease in cognitive function.

Am J Med. 2000 May;108(7):538-46.

PMID: 10806282 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10806282&dopt=Abstract

Cognitive impairment associated with atorvastatin and simvastatin.

King DS, Wilburn AJ, Wofford MR, Harrell TK, Lindley BJ, Jones DW.

Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi 39216, USA. dking@pharmacy.umsmed.edu

Pharmacotherapy. 2003 Dec;23(12):1663-7.

“we report two women who experienced significant cognitive impairment temporally related to statin therapy. One woman took atorvastatin, and the other first took atorvastatin, then was rechallenged with simvastatin. Clinicians should be aware of cognitive impairment and dementia as potential adverse effects associated with statin therapy.” PMID: 14695047

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14695047

Cognitive impairment associated with atorvastatin.

King DS, Jones DW, Wofford MR et al. (2001), Presented at the American College of Clinical Pharmacy Spring Practice and Research Forum. Salt Lake City; April 22-25.

Australian Adverse Drug Reactions Bulletin (Australia’s equivalent to the FDA)

Volume 17, Number 3, August 1998, section 3, page 3

Simvastatin is listed under “**DRUGS THAT MAKE YOU FORGET**”

Recognizing the 14 reports of Amnesia under that drug, .8% of the total adverse effects for that drug.

www.health.gov.au/tga/docs/pdf/aadrbltn/aadr9808.pdf

Statin-associated memory loss: analysis of 60 case reports and review of the literature.

Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM.

Drug Information Service, Duke University Medical Center, Durham, North Carolina 27710, USA. Pharmacotherapy. 2003 Jul;23(7):871-80.

This study searched the MedWatch drug surveillance system of the Food and Drug Administration (FDA) from November 1997-February 2002 for reports of statin-associated memory loss. They also reviewed the published literature. References from the study are good for follow-up research.

Abstract:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12885101&dopt=Abstract

Full Study Text free on Medscape:

<http://www.medscape.com/viewarticle/458867>

The Role of Lipid-Lowering Drugs in Cognitive Function: A Meta-Analysis of Observational Studies

from Pharmacotherapy

Posted 06/30/2003

Mahyar Etminan, Pharm.D., Sudeep Gill, M.D., FRCPC, Ali Samii, M.D., FRCPC

Although this study does bring the cognitive issues to light, it is a very poor study. The authors left out the pivotal study by Dr. Muldoon, that showed nearly 100% of statin users had a measurable loss of cognitive ability after 6 months, while 100% of the placebo group improved their scores.

Abstract:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12820814&dopt=Abstract

Full Study Text free on Medscape:

<http://www.medscape.com/viewarticle/456866>

Simvastatin-Associated Memory Loss

Amanda Orsi, Pharm.D., Olga Sherman, Pharm.D., and Zegga Woldelessie, Pharm.D.,

Abstract: The statins are widely used to treat dyslipidemias. They are generally associated with mild adverse effects, but rarely, more serious reactions may occur. A 51-year-old man experienced delayed-onset, progressive memory loss while receiving simvastatin for hypercholesterolemia. His therapy was switched to pravastatin, and memory loss resolved gradually over the next month, with no recurrence of the adverse effect.

from Pharmacotherapy

Posted 06/01/2001

Page 1 of 3:

<http://www.medscape.com/viewarticle/409738?WebLogicSession=PXke2H8h99pyNVS CajAh5clptzOAHJSZuNBobSwWmi9veWjdJ2A3%7C-1468812056489609316/184161392/6/7001/7001/7002/7002/7001/-1>

full printable version: http://www.medscape.com/viewarticle/409738_print

ADR of the Month

September 2001 Vol. 6 No. 9

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[http://hsc.virginia.edu/pharmacy-](http://hsc.virginia.edu/pharmacy-services/Newsletters/ADR%20of%20the%20Month/ADRMonth%209-01htm.html)

[services/Newsletters/ADR%20of%20the%20Month/ADRMonth%209-01htm.html](http://hsc.virginia.edu/pharmacy-services/Newsletters/ADR%20of%20the%20Month/ADRMonth%209-01htm.html)

The Tablet, a general member benefit published by the British Columbia Pharmacy Association, September 2001, Volume 10 no 8.

Excerpt:

Do HMG-CoA reductase inhibitors impair memory? After taking simvastatin for a year, a 51-year-old patient developed short term memory loss, to the extent of being unable to complete his sentences because he would forget what he was going to say. The drug was discontinued, replaced by pravastatin, and within one month his memory returned.¹⁴ In a separate case, a 67-year-old woman developed impaired short-term memory, altered mood, social impairment, cognitive impairment and dementia after one year of atorvastatin therapy. When atorvastatin was discontinued, her memory, mood and cognition improved completely.¹⁵ Memory impairment in a patient receiving atorvastatin has been reported to the BC Regional ADR Centre.

REFERENCES:

14. Orsi A, Sherman O, Woldeeslassie Z. Simvastatin-associated memory loss.

15. King DS, Jones DW, Wofford MR et al. **First report of cognitive impairment in an elderly patient: case report.** *Pharmacotherapy* 2001 Mar; 21: 371.

http://www.bcpharmacy.ca/publications/thetablet/pdf_version/BCPhA_Tablet-Sep2001.pdf

See page 11 of 16:

See also:

Statins and risk of polyneuropathy, A case-control study

D. Gaist, MD, PhD; U. Jeppesen, MD, PhD; M. Andersen, MD, PhD; L.A. García Rodríguez, MD, MSc;

J. Hallas, MD, PhD; and S.H. Sindrup, MD, PhD

<http://213.4.18.135/87.pdf> full text

Preclinical safety evaluation of cerivastatin, a novel HMG-CoA reductase inhibitor.

von Keutz E, Schluter G.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9737641&dopt=Abstract

Institute of Toxicology, PH-Product Development, Bayer AG, Wuppertal, Germany

Am J Cardiol. 1998 Aug 27;82(4B):11J-17J.

PMID: 9737641

“In dogs, the species most sensitive to statins, cerivastatin caused erosions and hemorrhages in the gastrointestinal tract, bleeding in the brain stem with fibroid degeneration of vessel walls in the choroid plexus, and lens opacity.”

Subchronic toxicity of atorvastatin, a hydroxymethylglutaryl-coenzyme A reductase inhibitor, in beagle dogs.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8864188&dopt=Abstract

Walsh KM, Albassam MA, Clarke DE.

Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48105, USA.

“The toxicity of atorvastatin (AT), an inhibitor of hydroxymethylglutaryl-coenzyme A reductase (HMG), was evaluated in beagle dogs... hemorrhage in gallbladder and brain, demyelination of optic nerve, and skeletal muscle necrosis”

Finally, on **memory loss and statins: Sworn testimony from the Baycol trial** in Corpus Christi, Texas. From the transcript of the AM Session on 03-05-03, in the case Hollis Haltom Vs. Bayer Corporation. Testifying under oath,, in response to the plaintiff’s attorney’s question, “What is your current position at Bayer?”, LAWRENCE POSNER, M.D of BAYER stated: “I’m the -- currently I’m the head of worldwide regulatory affairs for our prescription drug business, which means I have responsibility in somewhere between 60 and 100 countries where we sell products for registrations, compliance, things of that nature.” Excerpts from the trial transcript follow, with the Q indicating counsel’s Question, and the A indicating Dr. Posner’s Answer:

Q. So there are some concerns addressed here back in 1995 about testing up to .8. And do you know what the nature of the concern was?

A. Yes. It was related to a side effect that occurred in the brain.

Q. Of what kind of animal?

A. It occurred in the brain of dogs.

Q. Okay. So there was a side effect that occurred in dogs, and then there was a concern about whether you wanted to go forward and test at this higher dose level in human beings, given what you had learned about the dogs, right?

A. That's correct.

Q. Okay. Now, did you just say, well, let's forget about these concerns and we'll go ahead and put .8 on the market anyway, or did you do some further analysis that was not mentioned the other day?

A. Yes. The authors of this had -- they had two concerns. One concern was the toxicity that they found in the brain of dogs. But the other was that they had no way to identify this and who might be at risk before it happened. So there was no way to detect that someone was at risk for this side effect.

[skip some testimony on other topics]

Q. Do you remember in one kind of animal there had been some studies done that there could be a particular kind of problem with one kind of animal?

A. Oh, yeah. Yes, from the -- that's correct, from the toxicology studies.

Q. Okay. And were you able to demonstrate to your own satisfaction, to SmithKline's satisfaction, to the FDA's satisfaction, that that particular problem that showed up with that kind of animal is not something that happens in human beings?

A. Yes. We did it -- we did it by explaining the toxicology data. We also explained it on the basis of kinetic data. That actually at the higher levels of drug, what happens is a

certain amount of drug is bound to proteins in the body that circulate; and therefore, is not -- cannot cause side effects. And actually, a much smaller proportion of the drug is free. And that what you corrected for that, you actually found out that the margins of safety were in fact greater than you would predict just from the animal data.

Q. And as you move forward then and got approval and sold Baycol from 1997 through 2001, did that problem that had shown up with that one kind of animal ever become a problem with human beings?

A. It was actually shown with other statins as well. It wasn't unique to cerivastatin. It was a problem -- it was identified early on with lovastatin and some of the others. In fact, for none of the statins did it ever predict for any clinical problem or toxicity.

Q. So these animals would have that same problem regardless of which statin -- or at least with other statins?

A. Certainly with lovastatin it was true.

Q. But when it came time to human beings, that just wasn't something that happened to human beings?

A. And I think today no one pays much attention to it.

AMNESIA & STATINS

Frequently Asked Question: Amnesia is one of the Lipitor side effects reported by Pfizer on the Physician's Information, where can I find out more about people who have had amnesia episodes while taking the drug?

Lipitor, Thief of Memory, by Duane Graveline M.D.

Dr. Graveline, retired family MD, USAF Flight Surgeon, researcher in space medicine and US Astronaut, who suffered adverse effects from Lipitor, maintains several websites and is working on a second book about statin adverse effects, including statin-related memory loss and amnesia at:

www.spacedoc.net (you can start here and read about his life and his books)

http://www.spacedoc.net/lipitor_thief_of_memory.html

<http://www.spacedoc.net/lipitor.htm>

http://www.spacedoc.net/statin_dialogues.htm

Australian Adverse Drug Reactions Bulletin (Australia's equivalent to the FDA)

Volume 17, Number 3, August 1998, section 3, page 3

Simvastatin is listed under "DRUGS THAT MAKE YOU FORGET"

Recognizing the 14 reports of Amnesia under that drug, .8% of the total adverse effects for that drug.

www.health.gov.au/tga/docs/pdf/aadrbltn/aadr9808.pdf

CHEST PAIN & STATINS

Frequently Asked Question: Chest pain, that my cardiologist cannot explain via angiogram, stress test, EEG or EKG, is one of the side-effects I see is reported by many people. Is there any information on chest pain associated with statins?

Naturally, chest pain should be first evaluated by a cardiologist. If the usual explanations for chest pain do not apply to you, and you believe that statin adverse-effect may be the cause, here are some articles that may give you some background, or may be useful to give to your doctor. Some are specific to statins and cardiomyopathy, some are background on how statins affect CoQ10 production and how a CoQ10 deficiency affects the cells.

Most of these research articles have been found via a search of the National Institutes of Health website <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=&DB=PubMed> , a repository for hundreds of medical journals. In most cases, only the abstract is available and the full article must be purchased. Many of the others can be found via a Google or other net search, or were discovered via posts on the Lipitor message boards.

See:

<http://www.lipitor.com/pi/default.asp> Pfizer's **Physician's Info for prescribing Lipitor**, includes documented known adverse effects. Note "Body as a Whole: Chest pain," the italics indicate that the incidence was > 2% in original trials.

Phillips PS, Phillips CT, Sullivan MJ, Naviaux RK, Haas RH.

Statin myotoxicity is associated with changes in the cardiopulmonary function.

Atherosclerosis. 2004 Nov;177(1):183-8.

PMID: 15488882 [PubMed - in process]

Scripps Mercy Clinical Research Center, Scripps Mercy Hospital, Cardiology (Mer 74), Catheterization Laboratories, Scripps Mercy Hospital, 4077 Fifth Avenue, San Diego, CA 92103, USA. phillips.paul@scrippshealth.org

“The mechanism of the muscle toxicity associated with lipid-lowering therapy remains obscure. Pathological and biochemical findings in patients with statin myotoxicity suggest impaired fatty acid oxidation. Exhaled gas analysis can be used to assess substrate utilization including fatty acid oxidation. In order to determine if muscle toxicity due to lipid-lowering therapy might be related to abnormalities in lipid oxidation, exhaled gas analysis was performed in the fasted state on 11 patients subsequent to statin-associated myositis reactions. Results were compared to those of 16 normal controls who were measured both on and off statin therapy. Post-myositis patients showed a depressed anaerobic threshold (AT) (P=0.009) compared to controls while age-adjusted maximal oxygen consumption (VO₂max) and ventilatory efficiency (VE/VCO₂) were not significantly different. The fasting respiratory exchange ratio (RER) of post-myositis

patients off statins was abnormally increased ($P=0.00001$) as was their S1-slope ($P=0.023$). Controls demonstrated a significant increase in their RER while taking statins consistent with decreased lipid oxidation ($P < 0.00001$). These findings suggest that abnormal lipid oxidation in certain patients may predispose them to the myotoxicity caused by lipid-lowering therapies.”

1: Silver MA, Langsjoen PH, Szabo S, Patil H, Zelinger A.

Effect of atorvastatin on left ventricular diastolic function and ability of coenzyme Q10 to reverse that dysfunction.

Am J Cardiol. 2004 Nov 15;94(10):1306-10.

PMID: 15541254 [PubMed - indexed for MEDLINE]

“This study evaluated left ventricular diastolic function with Doppler echocardiography before and after statin therapy. Statin therapy worsened diastolic parameters in most patients; coenzyme Q(10) supplementation in patients with worsening diastolic function with statin therapy improved parameters of diastolic function.”

2: Silver MA, Langsjoen PH, Szabo S, Patil H, Zelinger A.

Statin cardiomyopathy? A potential role for Co-Enzyme Q10 therapy for statin-induced changes in diastolic LV performance: description of a clinical protocol.

Biofactors. 2003;18(1-4):125-7.

PMID: 14695927 [PubMed - indexed for MEDLINE]

“Lipid-lowering statins are thought to have a favorable safety profile. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting step of mevalonate synthesis. Mevalonate is the substrate for further synthesis of cholesterol and Co Enzyme Q10 (CoQ10). CoQ10 plays an important role during oxidative phosphorylation in the myocardial cell. Since myocardial diastolic function is a highly ATP dependent, we reasoned that early changes of diastolic function may be an early marker of ventricular dysfunction. METHODS: Patients who are to commence on statin therapy will be enrolled in the trial. Baseline measurements of plasma CoQ10, total cholesterol, LDL, HDL, CoQ10/LDL ratio, peak E, peak A velocities, E/A ratio, deceleration time, isovolumetric relaxation time, color M-mode propagation velocity will be performed and patients will then begin to take Oral atorvastatin (Lipitor, Parke-Davis) 20 mg daily for three to six months. All baseline measurement will be repeated after 3 to 6 months of statin therapy. Those patients demonstrating > 1 measurement of diastolic LV function that worsened during the 3 to 6 months of statin therapy will be supplemented with CoQ10 300 mg. daily for 3 months. A followup echocardiogram and blood CoQ10 level will be measured in patients who received CoQ10 supplementation. RESULTS: Statistical analysis will be performed using the paired t test to compare coenzyme levels and echocardiographic indices at baseline and after treatment and after supplementation.”

3: Langsjoen PH, Langsjoen AM.

The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10. A review of animal and human publications.

Biofactors. 2003;18(1-4):101-11. Review.

PMID: 14695925 [PubMed - indexed for MEDLINE]

“The depletion of the essential nutrient CoQ10 by the increasingly popular cholesterol lowering drugs, HMG CoA reductase inhibitors (statins), has grown from a level of concern to one of alarm. With ever higher statin potencies and dosages, and with a steadily shrinking target LDL cholesterol, the prevalence and severity of CoQ10 deficiency is increasing noticeably. An estimated 36 million Americans are now candidates for statin drug therapy. Statin-induced CoQ10 depletion is well documented in animal and human studies with detrimental cardiac consequences in both animal models and human trials. This drug-induced nutrient deficiency is dose related and more notable in settings of pre-existing CoQ10 deficiency such as in the elderly and in heart failure. Statin-induced CoQ10 deficiency is completely preventable with supplemental CoQ10 with no adverse impact on the cholesterol lowering or anti-inflammatory properties of the statin drugs. We are currently in the midst of a congestive heart failure epidemic in the United States, the cause or causes of which are unclear. As physicians, it is our duty to be absolutely certain that we are not inadvertently doing harm to our patients by creating a wide-spread deficiency of a nutrient critically important for normal heart function.”

STATINS & MITOCHONDRIAL CYTOPATHY, COENZYME Q10 (UBIQUINONE) DEFICIENCY CAUSED BY STATINS

Do statins cause a CoQ10 deficiency?

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12353945&dopt=Abstract

Study report: <http://www.annals.org/issues/v137n7/nts/200210010-00004.html>

Dr. Phillips study mentioned in a Wall Street Journal article (This is smooth muscle, not cardiac muscle.) Conclusion "statin therapy may be associated with increased oxidation injury...mild adverse effects of statins that are difficult to assess might be much more prevalent than widely considered "

<http://www.impostertrial.com> Is Myopathy Part Of Statin Therapy? Dr. Phillips study website, with info for Patient and Physician

Cohen & Gold, Mitochondrial Cytopathy in Adults: What we know so far

<http://www.ccjm.org/pdffiles/COHEN701.PDF>

(See "Heart" in table page 4, and section on page 7) CoQ10 If statins cause CoQ10 deficiency, and CoQ10 deficiency causes mitochondrial disease, what are the symptoms of mitochondrial disease? Heart pain is one of them.

**Oxidation Injury in Patients Receiving HMG-CoA Reductase Inhibitors:
Occurrence in Patients without Enzyme Elevation or Myopathy.**

US Patents: # 4,933,165

[http://patft.uspto.gov/netacgi/nph-](http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=4933165.WKU.&OS=PN/4933165&RS=PN/4933165)

[Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=4933165.WKU.&OS=PN/4933165&RS=PN/4933165](http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=4933165.WKU.&OS=PN/4933165&RS=PN/4933165)

see also subsequent related patents: Do a search by patent number at:

<http://patft.uspto.gov/netahtml/srchnum.htm>

for the following:

United States Patent 5,082,650

United States Patent 5,849,777

United States Patent 6,264,960

Merck Patent application stating that statins interfere with CoQ10 and that deficiency causes problems. They documented that they knew this about statins in 1989, 10 years before the 100+ deaths by Rhabdomyolysis!

<http://sites.huji.ac.il/malaria/maps/ubiquinonemetpath.html>

Malaria Parasite **Metabolic Pathways Ubiquinone Metabolism**

another version:

<http://www.stdgen.lanl.gov/stdgen/images/KEGG/00130.html>

DEFINITION Ubiquinone biosynthesis - Reference pathway. Diagram of the Ubiquinone (aka CoQ10) metabolic pathway, highlighting exactly where the Statins interrupt it. All of the 17 or so steps have to happen correctly for the body to produce CoQ10, but statins interrupt (or retard) this in step #2.

Introduction to the Citizen's petition to the FDA:

<http://www.vaccinationnews.com/DailyNews/July2002/StatinInduced8.htm> by Dr. Peter Langsjoen This is the introduction to the petition. (It is aimed at getting attention, and the wording may be more alarming than necessary.)

To the FDA: "**Citizen Petition To Change The Labeling For All Statin Drugs (Mevacor, Lescol, Pravachol, Zocor, Lipitor, And Advicor) Recommending Use Of 100-200mg Per Day Of Supplemental Co-Enzyme Q10 To Reduce The Risk Of Statin-Induced Myopathies (Including Cardiomyopathy And Congestive Heart Failure),**" by Dr. Julian Whitaker, MD: <http://www.fda.gov/ohrms/dockets/dailys/02/May02/052902/02p-0244-cp00001-01-vol1.pdf> or as html: [http://216.239.33.100/search?q=cache:4qAiX-YbZLYC:www.fda.gov/ohrms/dockets/dailys/02/May02/052902/02p-0244-cp00001-01-vol1.pdf+Statin-](http://216.239.33.100/search?q=cache:4qAiX-YbZLYC:www.fda.gov/ohrms/dockets/dailys/02/May02/052902/02p-0244-cp00001-01-vol1.pdf+Statin-Induced+Cardiomyopathy+Introduction+To+The+Citizen%27s+Petition+On+Statins&hl=en&ie=UTF-8)

[Induced+Cardiomyopathy+Introduction+To+The+Citizen%27s+Petition+On+Statins&hl=en&ie=UTF-8](http://216.239.33.100/search?q=cache:4qAiX-YbZLYC:www.fda.gov/ohrms/dockets/dailys/02/May02/052902/02p-0244-cp00001-01-vol1.pdf+Statin-Induced+Cardiomyopathy+Introduction+To+The+Citizen%27s+Petition+On+Statins&hl=en&ie=UTF-8)

Statin Depletion of CoQ10 is linked to heart problems.

Exhibit A of FDA Petition: "The clinical use of HMG CoA-reductase inhibitors (statins) and the associated depletion of the essential co-factor coenzyme Q10; a review of pertinent human and animal data." by Dr. Peter Langsjoen MD:

http://www.fda.gov/ohrms/dockets/dailys/02/May02/052902/02p-0244-cp00001-02-Exhibit_A-vol1.pdf

Effect of atorvastatin on left ventricular diastolic function and ability of coenzyme Q10 to reverse that dysfunction.

Silver MA, Langsjoen PH, Szabo S, Patil H, Zelinger A.

Am J Cardiol. 2004 Nov 15;94(10):1306-10.

Heart Failure Institute, Department of Medicine, Advocate Christ Medical Center, University of Illinois/Christ Cardiovascular Disease Fellowship Program, Oak Lawn, Illinois 60453, USA. marc.silver@advocatehealth.com

<marc.silver@advocatehealth.com>

”This study evaluated left ventricular diastolic function with Doppler echocardiography before and after statin therapy. Statin therapy worsened diastolic parameters in most patients; coenzyme Q(10) supplementation in patients with worsening diastolic function with statin therapy improved parameters of diastolic function.”

Examples of the heart and other problems associated with statin depletion of CoQ10.

1: Silver MA, Langsjoen PH, Szabo S, Patil H, Zelinger A.

Effect of atorvastatin on left ventricular diastolic function and ability of coenzyme Q10 to reverse that dysfunction.

Am J Cardiol. 2004 Nov 15;94(10):1306-10.

PMID: 15541254 [PubMed - indexed for MEDLINE]

2: Rundek T, Naini A, Sacco R, Coates K, DiMauro S.

Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke.

Arch Neurol. 2004 Jun;61(6):889-92.

PMID: 15210526 [PubMed - indexed for MEDLINE]

3: Ornato JP.

Questions & answers. I take a statin to lower my LDL (bad) cholesterol level, but I've heard statins inhibit the production of coenzyme Q10 (CoQ10). Should I take a CoQ10 supplement?

Health News. 2004 Apr;10(4):16. No abstract available.

PMID: 15088591 [PubMed - indexed for MEDLINE]

4: Silver MA, Langsjoen PH, Szabo S, Patil H, Zelinger A.

Statin cardiomyopathy? A potential role for Co-Enzyme Q10 therapy for statin-induced changes in diastolic LV performance: description of a clinical protocol.

Biofactors. 2003;18(1-4):125-7.

PMID: 14695927 [PubMed - indexed for MEDLINE]

5: Passi S, Stancato A, Aleo E, Dmitrieva A, Littarru GP.

Statins lower plasma and lymphocyte ubiquinol/ubiquinone without affecting other antioxidants and PUFA.

Biofactors. 2003;18(1-4):113-24.
PMID: 14695926 [PubMed - indexed for MEDLINE]

6: Langsjoen PH, Langsjoen AM.
The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10. A review of animal and human publications.
Biofactors. 2003;18(1-4):101-11. Review.
PMID: 14695925 [PubMed - indexed for MEDLINE]

7: Pettit FH, Harper RF, Vilaythong J, Chu T, Shive W.
Reversal of statin toxicity to human lymphocytes in tissue culture.
Drug Metabol Drug Interact. 2003;19(3):151-60.
PMID: 14682607 [PubMed - indexed for MEDLINE]

8: Wolters M, Hahn A.
Plasma ubiquinone status and response to six-month supplementation combined with multivitamins in healthy elderly women--results of a randomized, double-blind, placebo-controlled study.
Int J Vitam Nutr Res. 2003 May;73(3):207-14.
PMID: 12847998 [PubMed - indexed for MEDLINE]

9: Hargreaves IP.
Ubiquinone: cholesterol's reclusive cousin.
Ann Clin Biochem. 2003 May;40(Pt 3):207-18. Review.
PMID: 12803831 [PubMed - indexed for MEDLINE]

10: [No authors listed]
Extra co-enzyme Q10 for statin-users?
Treatmentupdate. 2001 Jun;13(2):4-7.
PMID: 11570288 [PubMed - indexed for MEDLINE]

11: Fosslien E.
Mitochondrial medicine--molecular pathology of defective oxidative phosphorylation.
Ann Clin Lab Sci. 2001 Jan;31(1):25-67. Review.
PMID: 11314862 [PubMed - indexed for MEDLINE]

12: Kaikkonen J, Nyysönen K, Tomasi A, Iannone A, Tuomainen TP, Porkkala-Sarataho E, Salonen JT.
Antioxidative efficacy of parallel and combined supplementation with coenzyme Q10 and d-alpha-tocopherol in mildly hypercholesterolemic subjects: a randomized placebo-controlled clinical study.
Free Radic Res. 2000 Sep;33(3):329-40.
PMID: 10993487 [PubMed - indexed for MEDLINE]

13: Levin WM.

Statin drugs: a double-edged sword?

Hosp Pract (Off Ed). 1997 Aug 15;32(8):44. No abstract available.
PMID: 9275961 [PubMed - indexed for MEDLINE]

14: De Pinieux G, Chariot P, Ammi-Said M, Louarn F, Lejonc JL, Astier A, Jacotot B, Gherardi R.

Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio.

Br J Clin Pharmacol. 1996 Sep;42(3):333-7.
PMID: 8877024 [PubMed - indexed for MEDLINE]

15: Fjelstrup A.

[Statin therapy and heart failure. There is a difference between statins]

Tidsskr Nor Laegeforen. 1994 May 20;114(13):1561-2. Norwegian. No abstract available.

PMID: 8079255 [PubMed - indexed for MEDLINE]

16: Carlsen SM, Fougner KJ.

[Statin therapy, Q10 and heart failure. Is there any difference between statins?]

Tidsskr Nor Laegeforen. 1994 Apr 30;114(11):1345. Norwegian. No abstract available.

PMID: 8079217 [PubMed - indexed for MEDLINE]

17: Hyams DE, Roylance PJ, Kruger K, Bodd E.

[Do we kill our cardiac patients with statin therapy? Coenzyme Q10, what do we know?]

Tidsskr Nor Laegeforen. 1994 Feb 20;114(5):590. Norwegian. No abstract available.

PMID: 7748252 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=247468&dopt=Abstract

Lovastatin decreases coenzyme Q levels in humans.

Proc Natl Acad Sci U S A. 1990 Nov;87(22):8931-4.

PMID: 2247468 [PubMed - indexed for MEDLINE] A 1990 study showing depletion of CoQ10 by Lovastatin – includes descriptions of cardiac patients.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1479481&dopt=Abstract A 2001 discussion on "The effect of pravastatin and atorvastatin on coenzyme Q10"

<http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/C/CellularRespiration.html>

Primer on how cells breathe normally (Note the role of CoQ10, called "Ubiquinone" in "The Respiratory Chain" section.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11505177&dopt=Abstract (abstract)

<http://213.4.18.135/70.pdf>

<http://216.239.33.100/search?q=cache:IGxCBJ3vs1kC:213.4.18.135/70.pdf+gaist+statin+myopathy+risk+greater&hl=en&ie=UTF-8> view as html

Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. Dr. Gaist is in Denmark and studies populations of entire countries for epidemiology information.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12011277&dopt=Abstract Dr. Gaist's study, **Statins and risk of polyneuropathy: a case-control study. (more serious than peripheral neuropathy)**

<http://213.4.18.135/87.pdf> Dr. Gaist's studies on Statin-induced nerve damage (full text)

Others:

Watts GF, Castelluccio C, Rice-Evans C, Taub NA, Baum H, Quinn PJ. **Plasma coenzyme Q (ubiquinone) concentrations in patients treated with simvastatin.**

J Clin Pathol. 1993;46:1055-7. [PMID: 8254097]

[http://www.ncbi.nlm.nih.gov/htbin-](http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&Dopt=r&uid=PMID:8254097)

[post/Entrez/query?db=m&form=6&Dopt=r&uid=PMID: 8254097](http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&Dopt=r&uid=PMID:8254097)

Mortensen SA, Leth A, Agner E, Rohde M. **Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase inhibitors.**

Mol Aspects Med. 1997;18 Suppl:S137-44. [PMID: 9266515]

[http://www.ncbi.nlm.nih.gov/htbin-](http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&Dopt=r&uid=9266515)

[post/Entrez/query?db=m&form=6&Dopt=r&uid=9266515](http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&Dopt=r&uid=9266515)

Bargossi AM, Grossi G, Fiorella PL, Gaddi A, Di Giulio R, Battino M. **Exogenous CoQ10 supplementation prevents plasma ubiquinone reduction induced by HMG-CoA reductase inhibitors.** Mol Aspects Med. 1994;15 Suppl:s187-93. [PMID: 7752830]

[http://www.ncbi.nlm.nih.gov/htbin-](http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&Dopt=r&uid=7752830)

[post/Entrez/query?db=m&form=6&Dopt=r&uid=7752830](http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&Dopt=r&uid=7752830)

Ogasahara S, Engel AG, Frens D, Mack D. **Muscle coenzyme Q deficiency in familial mitochondrial encephalomyopathy.** Proc Natl Acad Sci U S A. 1989;86:2379-82.

[PMID: 2928337] [http://www.ncbi.nlm.nih.gov/htbin-](http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&Dopt=r&uid=2928337)

[post/Entrez/query?db=m&form=6&Dopt=r&uid=2928337](http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&Dopt=r&uid=2928337)

Baker SK, Tarnopolsky MA. **Statin myopathies: pathophysiologic and clinical perspectives.** Clin Invest Med. 2001;24:258-72. [PMID: 11603510]

[http://www.ncbi.nlm.nih.gov/htbin-](http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&Dopt=r&uid=11603510)

[post/Entrez/query?db=m&form=6&Dopt=r&uid=11603510](http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&Dopt=r&uid=11603510)

Rosenfeldt FL, Pepe S, Ou R, Mariani JA, Rowland MA, Nagley P, et al. Coenzyme Q10 improves the tolerance of the senescent myocardium to aerobic and ischemic stress:

studies in rats and in human atrial tissue. Biofactors. 1999;9:291-9. [PMID: 10416043]

<http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&Dopt=r&uid=10416043>

Reust CS, Curry SC, Guidry JR. **Lovastatin use and muscle damage in healthy volunteers undergoing eccentric muscle exercise.** West J Med. 1991;154:198-200. [PMID: 2006566] <http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&Dopt=r&uid=2006566>

Statin-associated myopathy.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12672737&dopt=Abstract

Thompson PD, Clarkson P, Karas RH.

Preventive Cardiology and Cardiovascular Research, Division of Cardiology, Hartford Hospital, Hartford, Conn 06102, USA. pthomps@harthosp.org

“recent evidence suggests that statins reduce the production of small regulatory proteins that are important for myocyte maintenance”

Statins and myotoxicity.

Curr Atheroscler Rep. 2003 Mar;5(2):96-100. Review.

PMID: 12573193 Farmer JA.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12573193&dopt=Abstract

Baylor College of Medicine, One Baylor Plaza, Room 525D, Houston, TX 77030, USA. jfarmer@bcm.tmc.edu

CARNITINE DEFICIENCY CAUSED BY STATINS

Can statins cause carnitine deficiency?

Bhuiyan J, Seccombe DW. **The effects of 3-hydroxy-3-methylglutaryl-CoA reductase inhibition on tissue levels of carnitine and carnitine acyltransferase activity in the rabbit.** Lipids. 1996;31:867-70. [PMID: 8869889] <http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&Dopt=r&uid=8869889>

JOINT PAIN AND STATINS

Frequently Asked Question: Can statins have something to do with my joint pain?

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11707010&dopt=Abstract **Four cases of tendinopathy in patients on statin therapy.**

Joint Bone Spine. 2001 Oct;68(5):430-3. PMID: 11707010 [PubMed - indexed for MEDLINE]

Abstract on a report of 4 cases of people with painful tendons & statins. Included to show that the pain and damage shows up in a variety of areas.

QUITTING STATINS

Frequently Asked Question: Can it be dangerous to just stop taking statins?

One study indicated that there are more coronary events when people stop taking statins (Definitely talk with your doctor on this):

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11914253&dopt=Abstract **Withdrawal of statins increases event rates in patients with acute coronary syndromes. The dangers of getting off statins.** See also: http://www.lipidsonline.org/commentaries/al_abstract.cfm?abs_id=Abs030

STATIN BIRTH DEFECTS

Frequently Asked Question: Is statin intake during pregnancy dangerous for unborn children?

Edison RJ, Muenke M.

Central nervous system and limb anomalies in case reports of first-trimester statin exposure.

N Engl J Med. 2004 Apr 8;350(15):1579-82. No abstract available.

PMID: 15071140 [PubMed - indexed for MEDLINE]

VIOLENCE AND LOW CHOLESTEROL

Frequently Asked Questions: Can it be the statins making me so irritable and prone to angry outbursts?

It may be that the angry outbursts are caused by the Low Cholesterol, the result of taking Lipitor or other statins.

Dr. Beatrice Golomb, who is now conducting the NIH funded Statin Study, published 2 articles/studies on the connection between violence and low cholesterol levels.

See:

Golomb BA, Kane T, Dimsdale JA (2004), **Severe irritability associated with statin cholesterol-lowering drugs.** QJM 97(4):229-235.

Low cholesterol and violent crime. Golomb BA, Stattin H, Mednick S. Department of Medicine, University of California, Los Angeles, CA 92093-0995, USA. J Psychiatr Res 2000 Jul-Oct;34(4-5):301-9

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11104842&dopt=Abstract

and

Cholesterol and violence: is there a connection? Golomb BA. Ann Intern Med 1998 Mar 15;128(6):478-87

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9499332&dopt=Abstract

IMMUNE SYSTEM AND STATINS

Frequently Asked Question: Can statins depress my immune system?

It is a tribute to the imaginations of the drug marketers to see how successfully they have put positive “spin” on a very alarming proposition, that statins depress the immune system (or is it just arrogance?). If the known side effect of statins is to depress your immune system, and it is so beneficial to transplant recipients and others with autoimmune disease, what about people with pre-statin 'normal' immune systems? I'm not the only one astonished and disgusted with this, check out Dr. Mercola's comment (scroll down for his response to the article) on

<http://www.mercola.com/2000/dec/24/statins.htm>

Excerpts: "This is an amazing example of positive "spin" put on a very negative result. People with high cholesterol certainly don't need their immune systems suppressed...If suppressing the helper T cells is considered such great benefit then there is a disease going around that does this quite well - AIDS...if the mechanism of action of the drug is not understood, how can the manufacturer or the FDA claim that it is safe"

It sounds like he is talking about this article

http://pub.ucsf.edu/today/print.php?news_id=200211062 , but actually he is describing the last time the drug companies tried to feed us a myth about how great it is that statins depress immune systems: (available for online purchase from Nature Medicine:

<http://www.nature.com/dynasearch/app/dynasearch.taf?sp->

w=Exact&_action=search&search_fulltext=&sp-

p=All&search_volume=&search_startpage=&search_title=&search_author=&search_abstract=statins+as+immunosuppressors&issue_start_month=12&issue_start_year=2000&issue_end_month=01&issue_end_year=2001&pickerCount=You+have+selected+1+journal+to+search.&rolloverMessage=&sp_k=NM

Atorvastatin suppresses interferon-gamma -induced neopterin formation and tryptophan degradation in human peripheral blood mononuclear cells and in monocytic cell lines.

Neurauter G, Wirleitner B, Laich A, Schennach H, Weiss G, Fuchs D.

Summary: Recent findings indicate that statins also have anti-inflammatory properties and can modulate the immune response...statins inhibit T cell activation within the cellular immune response...atorvastatin directly inhibits IFN-gamma-mediated pathways in monocytic cells, suggesting that both immunoreactivity of T cells and of monocyte-derived macrophages are down-regulated by this statin.

Clin Exp Immunol 2003 Feb;131(2):264-7

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12562386&dopt=Abstract

A novel anti-inflammatory role for simvastatin in inflammatory arthritis.

Leung BP, Sattar N, Crilly A, Prach M, McCarey DW, Payne H, Madhok R, Campbell C, Gracie JA, Liew FY, McInnes IB.

J Immunol. 2003 Feb 1;170(3):1524-30.

PMID: 12538717 [PubMed - in process]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12538717&dopt=Abstract

Immunomodulation: a new role for statins?

Wulf Palinski

SUMMARY: Statins reduce the expression of the class II major histocompatibility complex (MHCII) by arterial cells, leading to a decreased T-cell response. This indicates that statins...

Nature Medicine6, 1311 - 1312 (01 Dec 2000) News and Views

HMG-CoA reductase inhibitors as immunomodulators: potential use in transplant rejection.

Raggatt LJ, Partridge NC.

These findings suggest that statins have the potential to regulate an immune response in vivo and that more investigation is essential in order to explain the opposing clinical data. Drugs. 2002;62(15):2185-91.

PMID: 12381218 [PubMed - in process]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12381218&dopt=Abstract

Statins as a newly recognized type of immunomodulator

Brenda Kwak, Flore Mulhaupt, Samir Myit, François Mach

SUMMARY: Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, or statins, are effective lipid-lowering agents, extensively used in medical practice. Statins have never been shown to...

Nature Medicine 6, 1399 - 1402 (01 Dec 2000) Article

***Could a depressed immune system lead to infection?* See:**

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11936540&dopt=Abstract

Statin-induced fibrotic nonspecific interstitial pneumonia.

Eur Respir J. 2002 Mar;19(3):577-80.

STATINS AND CANCER

Frequently Asked Question: What are the cancer rates for people on statins?

This new study breakthrough explains one mechanism that would explain why statins are associated with increased incidence of cancer.

Cholesterol is essential for cellular signaling - when the amount of cholesterol within the lipid domains gets too low, ERK becomes overactive.

Overactive ERK is associated with multiple cancers:

<http://www8.utsouthwestern.edu/utsw/cda/dept37389/files/210108.html>

DALLAS - March 3, 2005 - Cholesterol, often stigmatized for its role in heart disease, has long been known to be essential for the health of the fat-laden membranes that surround individual cells. New findings by researchers at UT Southwestern Medical Center highlight a novel role for cholesterol inside the cell itself - anchoring a signaling pathway linked to cell division and cancer.

These findings appear in the March 4 issue of Science and are available online.

"Cell signals have to be tightly controlled," said Dr. Richard G.W. Anderson, chairman of cell biology and senior author of the study. "If the signaling machines do not work, which can happen when the cell doesn't have enough cholesterol, the cell gets the wrong information, and disease results." Researchers discover a good side to cholesterol in controlling cell signals

The cell membrane, which is fluid in nature, contains cholesterol. Dr. Anderson's research focuses on regions of the membrane where cholesterol is enriched. These regions, called lipid domains, are more rigid than the rest of the cell membrane because of cholesterol and play a critical role in organizing signaling machinery at the cell surface. The correct arrangement of signaling modules in these domains is vital for communication inside the cell and is dependent on proper levels of cholesterol.

While studying how cholesterol moves to the membrane to get to lipid domains, Dr. Anderson, who holds the Cecil

H. Green Distinguished Chair in Cellular and Molecular Biology, and colleagues found that cholesterol can work outside the membrane to regulate a key signaling pathway that occurs inside the cell. Through an interaction with a protein called the oxysterol binding protein (OSBP), cholesterol holds together a group of enzymes that deactivates extracellular signal-related kinase (ERK). Overactive ERK is associated with multiple cancers.

When the amount of cholesterol in lipid domains is normal, the OSBP-cholesterol complex keeps the amount of active ERK under control. When cholesterol in the domains gets too low, however, the complex falls apart, leading to abnormally high levels of active ERK.

Dr. Anderson and colleagues noticed that OSBP has binding sites for both cholesterol and the other proteins in the complex. They believe that when cholesterol binds OSBP it changes shape to bind the key enzymes in a way that allows them to work together to control deactivation of ERK. When lipid domain cholesterol gets low, OSBP loses its cholesterol and no longer is able to bind the enzymes that deactivate ERK, keeping it active.

"OSBP appears to work like a cholesterol-regulated scaffolding protein that controls a key signaling pathway," Dr. Anderson said "This work shows a new way that lipids can regulate key signaling pathways and raises the possibility that other lipid regulated signaling scaffolds can malfunction in other diseases."

Other UT Southwestern contributors to the study were Dr. Jian Weng, assistant professor of cell biology, and Dr. Ping-Yuan Wang, postdoctoral researcher in cell biology and lead author.

This work was supported by the National Institutes of Health and the Perot Foundation.

[Photo caption:

Dr. Richard G.W. Anderson, chairman of cell biology at UT Southwestern (center), Dr. Ping-Yuan Wang, postdoctoral fellow (left), and Dr. Jian Weng, assistant professor of cell biology, have discovered that cholesterol anchors a signaling pathway linked to cell division and cancer.

Women and statins "in women from the age of 50 onward only, low cholesterol was significantly associated with all-cause mortality, showing significant associations with death through cancer, liver diseases, and mental diseases."

The abstract:

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstr>

[act&list_uids=15006277](#)

Why Eve is not Adam: prospective follow-up in 149650 women and men of cholesterol and other risk factors related to cardiovascular and all-cause mortality.

Ulmer H, Kelleher C, Diem G, Concin H.

J Womens Health (Larchmt). 2004 Jan-Feb;13(1):41-53.

Institute of Biostatistics and Documentation, Leopold Franzens University of Innsbruck, Innsbruck, Austria. Hanno.Ulmer@uibk.ac.at

PURPOSE: To assess the impact of sex-specific patterns in cholesterol levels on all-cause and cardiovascular mortality in the Vorarlberg Health Monitoring and Promotion Programme (VHM&PP). **METHODS :** In this study, 67413 men and 82237 women (aged 20-95 years) underwent 454448 standardized examinations, which included measures of blood pressure, height, weight, and fasting samples for cholesterol, triglycerides, gamma-glutamyl transferase (GGT), and glucose in the 15-year period 1985-1999. Relations between these variables and risk of death were analyzed using two approaches of multivariate analyses (Cox proportional hazard and GEE models). **RESULTS:** Patterns of cholesterol levels showed marked differences between men and women in relation to age and cause of death. The role of high cholesterol in predicting death from coronary heart disease could be confirmed in men of all ages and in women under the age of 50. In men, across the entire age range, although of borderline significance under the age of 50, and in women from the age of 50 onward only, low cholesterol was significantly associated with all-cause mortality, showing significant associations with death through cancer, liver diseases, and mental diseases. Triglycerides > 200 mg/dl had an effect in women 65 years and older but not in men. **CONCLUSIONS:** This large-scale population-based study clearly demonstrates the contrasting patterns of cholesterol level in relation to risk, particularly among those less well studied previously, that is, women of all ages and younger people of both sexes. For the first time, we demonstrate that the low cholesterol effect occurs even among younger respondents, contradicting the previous assessments among cohorts of older people that this is a proxy or marker for frailty occurring with age.

PMID: 15006277 [PubMed - indexed for MEDLINE]

Despite the infomercial-type hype in recent press releases under titles like, “Does Lipitor prevent cancer?” (note it is a question, not an assertion), the numbers from recent studies tell the opposite story:

Statin use and the risk of breast cancer.

Beck P, Wysowski DK, Downey W, Butler-Jones D.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12725884&dopt=Abstract

J Clin Epidemiol. 2003 Mar;56(3):280-5.

PMID: 12725884 [PubMed - in process]

“Stratified analyses revealed increases in risk in short-term statin users and statin users with long-term hormone replacement therapy (HRT) exposure.”

The PROSPER Study (PROspective study of pravastatin in the elderly at risk)

[Article in French]

Kulbertus H, Scheen AJ.

Service de Diabetologie, Nutrition et Maladies metaboliques et deMedecine Interne Generale, CHU Liege.

Rev Med Liege. 2002 Dec;57(12):809-13.

“New cancers were more frequent amongst pravastatin-treated individuals (+25%; p = 0.020).”

Major Outcomes in Moderately Hypercholesterolemic, Hypertensive Patients

Randomized to Pravastatin vs Usual Care

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12479764&dopt=Abstract

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.

Deaths by cancer during the ALLHAT study: Pravastatin= 163; Usual Care= 148

6-year rate per 100 Participants: Pravastatin= 4.1; Usual Care= 3.7

ERECTILE DYSFUNCTION (ED) AND STATINS

Frequently Asked Question: Can statins interfere with my sex life?

Do lipid-lowering drugs cause erectile dysfunction? A systematic review.

Rizvi K, Hampson JP, Harvey JN.

University of Wales College of Medicine, Wrexham Academic Unit, Wrexham, UK.

Fam Pract. 2002 Feb;19(1):95-8. PMID: 11818357

BACKGROUND: Erectile dysfunction (ED) is common although under-reported by patients. Along with the better known causes of ED, drug-induced impotence needs to be considered as a cause of this symptom. Lipid-lowering drugs have been prescribed increasingly. Their relationship to ED is controversial. **OBJECTIVES:** Our aim was to clarify the relationship between lipid-lowering therapy and ED. A secondary aim was to assess the value of the systematic review procedure in the area of adverse drug reactions. **METHODS:** A systematic review was carried out using computerized biomedical

databases and Internet sources. Terms denoting ED were linked with terms referring to lipid-lowering drugs. Information was also sought from regulatory agencies. RESULTS: A significant literature was identified, much from obscure sources, which included case reports, review articles, and information from clinical trials and from regulatory agencies. Information from all of these sources identified fibrates as a source of ED. A substantial number of cases of ED associated with statin usage have been reported to regulatory agencies. Case reports and clinical trial evidence supported the suggestion that statins can also cause ED. Some information on possible mechanisms was obtained, but the mechanism remains uncertain. CONCLUSIONS: The systematic review procedure was applied successfully to collect evidence suggesting that both statins and fibrates may cause ED. More numerous reports to regulatory agencies complemented more detailed information from case reports to provide a new perspective on a common area of prescribing.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11818357&dopt=Abstract

ERECTILE DYSFUNCTION AND STATIN THERAPY: INTERACTION WITH CARDIOVASCULAR RISK FACTORS AND DRUG THERAPIES

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Erectile dysfunction has been associated with atherosclerotic risk factors and drugs used in their treatment. This study investigated the relationship of erectile function with cardiovascular risk factors and specific drug therapies. International Index of Erectile Function (IIEF) scores measured in 100 men attending cardiovascular risk clinics. Cardiovascular risk factors and drug therapies were assessed prior to initiation and after 6 months of statin therapy. Before statin therapy no correlation was observed between IIEF score and any individual cardiovascular risk factor though better scores were observed in patients on warfarin or angiotensin-II receptor blocker therapy ($r=0.42$; $p < 0.001$). After 6 months of statin therapy, significant correlations were observed between lower IIEF scores ($r=0.62$; $P < 0.001$) and age, smoking, diabetes and usage of warfarin or angiotensin-2 type 1 receptor blocker (ARB) therapy. Differences in dose, relative efficacy or relative lipophilicity of statin prescribed showed no correlation with change in IIEF score. This study suggests impotence following statin therapy is likelier in patients with more severe endothelial dysfunction due to established cardiovascular risk factors including age, and smoking and diabetes. This is complicated by adverse interactions between statin therapy and concomitant treatment with warfarin or angiotensin-II type I receptor blockers.

<http://www.kenes.com/73eas/program/abstracts/126.doc>

Drug Information Center: Information on Statin Drugs

“On March 7, 2002, Colorado HealthSite interviewed Beatrice A. Golomb, MD, PhD, principal investigator of a study on Statin Drugs by the National Institutes of Health. Dr. Golomb noted that the most common problems reported about statin drugs pertain to muscle pain or weakness, fatigue, memory and cognitive problems, sleep problems, and neuropathy. Erectile dysfunction, problems with temperature regulation (feeling hot or cold, or having sweats) are among the other problems reported. “
<http://www.coloradohealthsite.org/pharmacology/statins.html>

“Question: What are the common complaints of patients who take statins?
Dr. Golomb: The most common problems we hear reported pertain to muscle pain or weakness, fatigue, memory and cognitive problems, sleep problems, and neuropathy. Erectile dysfunction, problems with temperature regulation (feeling hot or cold, or having sweats), are among the other problems reported. ”
<http://www.coloradohealthsite.org/topics/interviews/golomb.html>

BBC News: Wednesday, 15 March, 2000, 19:02 GMT

Heart drug impotence warning

"Statins prevent heart attacks by reducing the levels of dangerous cholesterol in the bloodstream.

However, a small number of men prescribed the life-saving drug have complained that they are unable to achieve an erection."

"Dr John Harvey, from the Wrexham Maelor Hospital in Wales, identified 220 men who appeared to have lost their "virility" after starting to take statins. "

<http://news.bbc.co.uk/1/hi/health/678811.stm>

Bailey DG, Dresser GK.

Interactions between grapefruit juice and cardiovascular drugs.

Am J Cardiovasc Drugs. 2004;4(5):281-97. Review.

PMID: 15449971 [PubMed - indexed for MEDLINE]

Blumentals WA, Brown RR, Gomez-Caminero A.

Antihypertensive treatment and erectile dysfunction in a cohort of type II diabetes patients.

Int J Impot Res. 2003 Oct;15(5):314-7.

PMID: 14562130 [PubMed - indexed for MEDLINE]

LUPUS-LIKE SYMPTOMS AND STATINS

Frequently Asked Question: Can statins cause Lupus symptoms?

Drug-induced lupus-like syndrome associated with severe autoimmune hepatitis.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12765306&dopt=Abstract

Graziadei IW, Obermoser GE, Sepp NT, Erhart KH, Vogel W.

Lupus. 2003;12(5):409-12.

PMID: 12765306 [PubMed - in process]

“Atorvastatin and other members of the statin family are widely used for the treatment of hypercholesterolaemia in order to reduce the risk of atherosclerosis and cardiovascular disease. Atorvastatin-induced adverse events are mostly mild and only a few cases of lupus-like syndrome or severe acute hepatitis have been documented. In this case report we describe a patient who developed an atorvastatin-induced severe autoimmune hepatitis. In addition, this patient presented with a concomitant systemic lupus-like syndrome which has been already described for statins but not in association with severe liver disease. Although the drug was immediately withdrawn the disease persisted and even deteriorated to a fulminant disease with evidence of acute hepatic failure. The patient failed to respond to conventional immunosuppression with corticosteroids and azathioprine. Only the introduction of intense immunosuppressive therapy, as used in solid organ transplantation, led to a complete and sustained recovery of the patient. Interestingly, the patient was HLA DR3- and HLA DR4-positive, which are well-known genetic factors associated with autoimmune diseases. This case is the first report of a drug-induced lupus-like syndrome concomitant with a severe autoimmune hepatitis in a genetically predisposed patient.”

Noel B, Panizzon RG.

Lupus-like syndrome associated with statin therapy.

Dermatology. 2004;208(3):276-7.

PMID: 15118389 [PubMed - indexed for MEDLINE]

“Statins are among the most widely prescribed drugs. An increasing number of lupus-like syndrome has recently been reported with these lipid-lowering agents. We describe a new case associated with simvastatin therapy. The presence of anti-dsDNA antibodies in the serum is for the first time reported confirming that statins may also induce a systemic autoimmune reaction. Statin-induced lupus-like syndrome is characterized by the long delay between the beginning of therapy and the skin eruption. Antinuclear antibodies may persist for many months after drug discontinuation. The causal relationship may be therefore difficult to establish, and probably many cases are unrecognized. Early diagnosis may avoid unnecessary immunosuppressive therapy. Copyright 2004 S. Karger AG, Basel”

Lantuejoul S, Brambilla E, Brambilla C, Devouassoux G.

Statin-induced fibrotic nonspecific interstitial pneumonia.

Eur Respir J. 2002 Mar;19(3):577-80.

PMID: 11936540 [PubMed - indexed for MEDLINE]

“Statins inhibit the 3-hydroxy-3-methylglutaryl coenzyme A reductase, reduce the serum level of low-density lipoprotein cholesterol, and are extensively prescribed to prevent cardiovascular mortality and morbidity. Few systemic adverse effects, such as pseudopolymyositis, lupus-like syndromes, and anecdotal hypersensitivity pneumonitis,

have been reported. A simvastatin-induced diffuse interstitial pneumonia associated with a nonspecific interstitial pneumonia pattern at histological analysis is reported here. Ultrastructural analysis showed a diffuse cytoplasmic accumulation of intralysosomal lamellar inclusions in type II pneumonocytes, histiocytes and endothelial cells, suggesting a shared pathogenesis with amphiphilic drug-induced toxic lung injury. Because statins are increasingly prescribed, statin-induced interstitial lung disorders may be more frequently observed and early recognition will be required.”

Chazerain P, Hayem G, Hamza S, Best C, Ziza JM.

Four cases of tendinopathy in patients on statin therapy.

Joint Bone Spine. 2001 Oct;68(5):430-3.

PMID: 11707010 [PubMed - indexed for MEDLINE]

“During the last decade, statins have been widely prescribed as lipid-lowering drugs. Their overall safety profile is good. The main musculoskeletal side effects have consisted of muscle pain and weakness, peripheral neuropathy, and a few cases of drug-induced lupus. We report the first four cases of tendinopathy in patients receiving statin therapy. There were three men and one woman. The diagnoses were extensor tenosynovitis at the hands (case 1), tenosynovitis of the tibialis anterior tendon (case 2), and Achilles tendinopathy (cases 3 and 4). Two patients were on simvastatin and two on atorvastatin. The tendinopathy developed 1 to 2 months after treatment initiation. The outcome was consistently favorable within 1 to 2 months after discontinuation of the drug. Similar cases have been reported to French pharmacovigilance centers. This report of four cases of tendinopathy draws attention to a possible and heretofore unrecognized side effect of a drug class that is becoming increasingly popular. Statins are effective in lowering high cholesterol levels in patients with type IIa or IIb hypercholesterolemia. They have been widely used for the last decade, particularly in the secondary and primary prevention of major coronary events. Statins act by inhibiting the enzyme hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. Although most patients tolerate statins extremely well, a few experience side effects requiring treatment discontinuation. Reported musculoskeletal side effects include myalgia and a few cases of rhabdomyolysis and polymyositis. Induced lupus and peripheral neuropathy are exceedingly rare.”

MYOPATHY AND STATINS

Frequently Asked Question: Do statins cause muscle damage, muscle pain, myopathy, myositis, and muscle cell death (apoptosis) with or without elevated CK?

1: Phillips PS.

Ezetimibe and statin-associated myopathy.

Ann Intern Med. 2004 Oct 19;141(8):649. No abstract available.

PMID: 15492351 [PubMed - indexed for MEDLINE]

2: Phillips PS, Phillips CT, Sullivan MJ, Naviaux RK, Haas RH.
Statin myotoxicity is associated with changes in the cardiopulmonary function.
Atherosclerosis. 2004 Nov;177(1):183-8.
PMID: 15488882 [PubMed - in process]

3: Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ, Vladutiu GD, England JD; Scripps Mercy Clinical Research Center.
Statin-associated myopathy with normal creatine kinase levels.
Ann Intern Med. 2002 Oct 1;137(7):581-5.
PMID: 12353945 [PubMed - indexed for MEDLINE]

And more:

Search terms "**STATIN + MYOPATHY**":

1: Koller H, Neuhaus O, Schroeter M, Hartung HP.
[Myopathies under therapy with lipid-lowering agents.]
Nervenarzt. 2004 Dec 18; [Epub ahead of print] German.
PMID: 15609055 [PubMed - as supplied by publisher]

2: [No authors listed]

A warning about one statin at a high dose.
Heart Advis. 2004 Nov;7(11):2. No abstract available.
PMID: 15580669 [PubMed - indexed for MEDLINE]

3: Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, Gurwitz JH, Chan KA, Goodman MJ, Platt R.
Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs.
JAMA. 2004 Dec 1;292(21):2585-90. Epub 2004 Dec 1.
PMID: 15572716 [PubMed - indexed for MEDLINE]

4: [No authors listed]

Safety of aggressive statin therapy.
Med Lett Drugs Ther. 2004 Nov 22;46(1196):93-5.
PMID: 15557874 [PubMed - indexed for MEDLINE]

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Prescription of statins to dyslipidemic patients affected by liver diseases: a subtle balance between risks and benefits.
Nutr Metab Cardiovasc Dis. 2004 Aug;14(4):215-24.
PMID: 15553600 [PubMed - in process]

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[Hypertriglyceridemia--diagnostics, risk and treatment]
Tidsskr Nor Laegeforen. 2004 Nov 4;124(21):2746-9. Review. Norwegian.

PMID: 15534665 [PubMed - indexed for MEDLINE]

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Rosuvastatin in the management of hyperlipidemia.

Clin Ther. 2004 Sep;26(9):1368-87.

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Is there value in liver function test and creatine phosphokinase monitoring with statin use?

Am J Cardiol. 2004 Nov 4;94(9A):30F-34F. Review.

PMID: 15519289 [PubMed - indexed for MEDLINE]

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Statins induce apoptosis in rat and human myotube cultures by inhibiting protein geranylgeranylation but not ubiquinone.

Toxicol Appl Pharmacol. 2004 Nov 1;200(3):237-50.

PMID: 15504460 [PubMed - indexed for MEDLINE]

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Rosuvastatin safety: lessons from the FDA review and post-approval surveillance.

Expert Opin Drug Saf. 2004 Nov;3(6):547-57.

PMID: 15500414 [PubMed - in process]

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Ezetimibe and statin-associated myopathy.

Ann Intern Med. 2004 Oct 19;141(8):649. No abstract available.

PMID: 15492351 [PubMed - indexed for MEDLINE]

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Risk of adverse events with fibrates.

Am J Cardiol. 2004 Oct 1;94(7):935-8.

PMID: 15464682 [PubMed - indexed for MEDLINE]

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Cytoskeletal myotoxicity from simvastatin and colchicine.

Muscle Nerve. 2004 Dec;30(6):799-802.

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Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial.

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Eur J Anaesthesiol. 2004 Jul;21(7):572-4. No abstract available.
PMID: 15318472 [PubMed - indexed for MEDLINE]

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McArdle's disease diagnosed following statin-induced myositis.
Ann Clin Biochem. 2004 Jul;41(Pt 4):338-40.
PMID: 15298748 [PubMed - in process]

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Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy.
Pharmacoepidemiol Drug Saf. 2004 Jul;13(7):417-26.
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The cerivastatin withdrawal crisis: a "post-mortem" analysis.
Health Policy. 2004 Aug;69(2):151-7.
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Safety of statins: focus on clinical pharmacokinetics and drug interactions.

Circulation. 2004 Jun 15;109(23 Suppl 1):III50-7. Review.

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Extended-release niacin for modifying the lipoprotein profile.

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A prospective study of pravastatin in the elderly at risk: new hope for older persons.

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Successful reintroduction of statin therapy after myositis: was there another cause?

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Ezetimibe and statin-associated myopathy.

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PMID: 15096354 [PubMed - indexed for MEDLINE]

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Rhabdomyolysis in association with simvastatin and amiodarone.

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Professional athletes suffering from familial hypercholesterolaemia rarely tolerate statin treatment because of muscular problems.
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Am J Health Syst Pharm. 2004 Mar 1;61(5):515-9. Review. No abstract available.
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Potential drug interaction between simvastatin and danazol causing rhabdomyolysis.
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PMID: 14712320 [PubMed - indexed for MEDLINE]

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Rhabdomyolysis induced by a single dose of a statin.

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Efficacy of fenofibrate and simvastatin on endothelial function and inflammatory markers in patients with combined hyperlipidemia: relations with baseline lipid profiles.

Atherosclerosis. 2003 Oct;170(2):315-23.

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Are statins indicated for the primary prevention of CAD in octogenarians? antagonist viewpoint.

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Effectiveness of statin-gemfibrozil combination therapy in patients with mixed hyperlipidemia: experience of a community lipid clinic and safety review from the literature.

Prev Cardiol. 2003 Fall;6(4):189-94.

PMID: 14605512 [PubMed - indexed for MEDLINE]

45: Pasternak R.

Ask the doctor. I am a 64-year-old woman with high cholesterol caused by bad genes (familial hypercholesterolemia). Without medication, my cholesterol is above 450 mg/dL. So I am taking high-dose Lipitor (80 mg/day), WelChol, and Zetia to lower my cholesterol. I sometimes have pain and stiffness in my knees, and my shoulder, elbow, and wrist joints, plus the muscles in between, are stiff in the morning and hurt during the day. Two years ago I was diagnosed with bursitis in my hips. Could these problems be from the Lipitor? If so, is there another statin I could take that wouldn't do this?

Harv Heart Lett. 2003 Oct;14(2):8. No abstract available.
PMID: 14576039 [PubMed - indexed for MEDLINE]

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The safety of HMG-CoA reductase inhibitors in special populations at high cardiovascular risk.

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Anaesthetic management of coronary artery bypass grafting in a patient with central core disease and susceptibility to malignant hyperthermia on statin therapy.

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Safety of atorvastatin derived from analysis of 44 completed trials in 9,416 patients.

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[Skeletal myopathy associated with concomitant use of statin and cyclosporin in a heart transplant patient - case report]

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Controversy surrounding the safety of cerivastatin.

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Combination lipid-lowering therapy with statins: safety issues in the postcerivastatin era.

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AIDS Rev. 2003 Jan-Mar;5(1):19-24. Review.

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Int J Cardiol. 2003 Jul;90(1):15-21. Review.

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Statin-associated myopathy with normal creatine kinase levels.

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RHABDOMYOLYSIS AND STATINS

Frequently Asked Question: Which statins cause deadly Rhabdomyolysis?

All of them. See :

FDA adverse event reports on statin-associated rhabdomyolysis.

Omar MA, Wilson JP.

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PMID: 11847951

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11847951&dopt=Abstract

Of 871 reports detailing 601 cases in a 29 month time frame, the list of statin, number of cases, and percentage of the whole follows:

simvastatin, 215 (35.8%);

cerivastatin, 192 (31.9%);

atorvastatin, 73 (12.2%);

pravastatin, 71 (11.8%);
lovastatin, 40 (6.7%);
fluvastatin, 10 (1.7%)

As of August, 2001, there were at least 81 rhabdomyolysis deaths associated with Non-Baycol statins. <http://www.essentialdrugs.org/edrug/archive/200108/msg00064.php>

The Public Citizen petition to the FDA, August 20, 2001:

<http://www.citizen.org/publications/release.cfm?ID=7051>

At that time the count of deaths by statin-induced rhabdomyolysis:

Outcome	Number of Cases	Percent of Total Deaths
Deaths		
Atorvastatin	13	18.1%
Cerivastatin	20	27.8%
Fluvastatin	1	1.4%
Lovastatin	5	6.9%
Pravastatin	9	12.5%
Simvastatin	24	33.3%

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Safety of HMG-CoA reductase inhibitors: focus on atorvastatin.

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Metabolism and drug interactions of 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors (statins).

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PMID: 9294990 [PubMed - indexed for MEDLINE]

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STATINS AND LIVER OR KIDNEY DAMAGE

Frequently Asked Question: Do statins damage liver or kidneys?

Kaplowitz N.

Statin-induced hepatotoxicity.

Gastroenterology. 2004 Oct;127(4):1278; author reply 1278-9. No abstract available.
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Apoptotic injury in cultured human hepatocytes induced by HMG-CoA reductase inhibitors.

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Statins and liver toxicity: a meta-analysis.

Pharmacotherapy. 2004 May;24(5):584-91. Review.
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[Information regarding adverse drug effects and treatment indications ("package inserts") exemplified by cervistatin (Lipobay)]

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PMID: 12658968 [PubMed - indexed for MEDLINE]

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Rhabdomyolysis with concurrent atorvastatin and diltiazem.

Ann Pharmacother. 2002 Oct;36(10):1546-9.
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Statin specific toxicity in organ transplant recipients: case report and review of the literature.

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PMID: 12113605 [PubMed - indexed for MEDLINE]

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PMID: 11173785 [PubMed - indexed for MEDLINE]

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A case with severe rhabdomyolysis and renal failure associated with cerivastatin-gemfibrozil combination therapy--a case report.

Angiology. 2000 Aug;51(8):695-7.

PMID: 10959522 [PubMed - indexed for MEDLINE]

ELDERLY AND STATINS

Frequently Asked Question: Should people over 70 take statins?

Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years.

JAMA. 1994 Nov 2;272(17):1335-40.

Krumholz HM, Seeman TE, Merrill SS, Mendes de Leon CF, Vaccarino V, Silverman DI, Tsukahara R, Ostfeld AM, Berkman LF.

Department of Internal Medicine, Yale University School of Medicine, New Haven, CT 06520-8017.

"CONCLUSIONS--Our findings do not support the hypothesis that hypercholesterolemia or low HDL-C are important risk factors for all-cause mortality, coronary heart disease mortality, or hospitalization for myocardial infarction or unstable angina in this cohort of persons older than 70 years."

Another study showing people over 65 do not benefit from cholesterol reduction:

Long-Term Prognostic Importance of Total Cholesterol in Elderly Survivors of an Acute Myocardial Infarction: The Cooperative Cardiovascular Pilot Project.

Foody JM, Wang Y, Kiefe CI, Ellerbeck EF, Gold J, Radford MJ, Krumholz HM. Section of Cardiovascular Medicine, Department of Medicine, and Section of Chronic Disease Epidemiology, Department of Epidemiology and Public Health, Yale School of Medicine, New Haven, Connecticut; Qualidigm, Middletown, Connecticut; Yale-New Haven Hospital Center for Outcomes Research and

Evaluation, New Haven, Connecticut; Center for Outcome and Effectiveness Research and Education, University of Alabama at Birmingham and Birmingham Veterans Affairs Medical Center, Birmingham, Alabama; Department of Preventive Medicine, University of Kansas School of Medicine, Kansas City, Kansas; and Metastar, Madison, Wisconsin.
J Am Geriatr Soc. 2003 Jul;51(7):930-936. PMID: 12834512

"PARTICIPANTS: Four thousand nine hundred twenty-three Medicare beneficiaries from four states aged 65 and older"

"CONCLUSION: Among elderly survivors of AMI, elevated total serum cholesterol measured postinfarction is not associated with an increased risk of all-cause mortality in the 6 years after discharge. Furthermore, this study found no evidence of an increased risk of all-cause mortality in patients with low total cholesterol. Further studies are needed to determine the relationship of postinfarction lipid subfractions and mortality in older patients with coronary artery disease (CAD)."

High-density vs low-density lipoprotein cholesterol as the risk factor for coronary artery disease and stroke in old age.

Weverling-Rijnsburger AW, Jonkers IJ, van Exel E, Gussekloo J, Westendorp RG. Section of Gerontology and Geriatrics, Department of General Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands. a.w.e.weverling-rijnsburger@lumc.edu
Arch Intern Med. 2003 Jul 14;163(13):1549-54.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12860577&dopt=Abstract

"In contrast to high LDL cholesterol level, low HDL cholesterol level is a risk factor for mortality from coronary artery disease and stroke in old age."

Total cholesterol and risk of mortality in the oldest old.

Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG. Department of General Internal Medicine, Leiden University Medical Center, The Netherlands.
Lancet. 1997 Oct 18;350(9085):1119-23.

" In people older than 85 years, high total cholesterol concentrations are associated with longevity owing to lower mortality from cancer and infection. The effects of cholesterol-lowering therapy have yet to be assessed."

Golomb BA, Criqui MH, White HL, Dimsdale JE.

The UCSD Statin Study: a randomized controlled trial assessing the impact of statins on selected noncardiac outcomes.

Control Clin Trials. 2004 Apr;25(2):178-202.
PMID: 15020036 [PubMed - indexed for MEDLINE]

Algotsson A, Winblad B.

Patients with Alzheimer's disease may be particularly susceptible to adverse effects of statins.

Dement Geriatr Cogn Disord. 2004;17(3):109-16. Epub 2004 Jan 20. Review.
PMID: 14739530 [PubMed - indexed for MEDLINE]

IS THERE AN INDUSTRY BIAS IN STATIN PUBLICATIONS?

Why are most studies so positive about statins, and why are there relatively so few published that show problems? Do Medical Journals agree that there is bias in drug-industry funded medical studies?

Yes, as does an observational study.

Association of Funding and Conclusions in Randomized Drug Trials A Reflection of Treatment Effect or Adverse Events?

<http://jama.ama-assn.org/cgi/content/abstract/290/7/921>

Bodil Als-Nielsen, MD; Wendong Chen, MD; Christian Gluud, MD, DMSc; Lise L. Kjaergard, MD

JAMA. 2003;290:921-928 Vol 290 No 7, August 20, 2003

"The experimental drug was recommended as treatment of choice in 16% of trials funded by nonprofit organizations, 30% of trials not reporting funding, 35% of trials funded by both nonprofit and for-profit organizations, and 51% of trials funded by for-profit organizations ($P < .001$; 2 test). Logistic regression analyses indicated that funding, treatment effect, and double blinding were the only significant predictors of conclusions. Adjusted analyses showed that trials funded by for-profit organizations were significantly more likely to recommend the experimental drug as treatment of choice (odds ratio, 5.3; 95% confidence interval, 2.0-14.4) compared with trials funded by nonprofit organizations. This association did not appear to reflect treatment effect or adverse events. "

"Conclusions Conclusions in trials funded by for-profit organizations may be more positive due to biased interpretation of trial results. Readers should carefully evaluate whether conclusions in randomized trials are supported by data. "

"Author Affiliations: The Copenhagen Trial Unit, Center for Clinical Intervention Research, Copenhagen University Hospital, Copenhagen, Denmark."

Clearly JAMA came to the conclusion that funding biases the findings in 2002, when they quite publicly changed their editorial policy to require funding information for studies they publish.

Further, you are invited to view the British Journal of Medicine, May 31, 2003 (Volume 326, Issue 7400), which has focused attention on bias and spin in industry-sponsored studies. They carried the following articles at
<http://bmj.com/content/vol326/issue7400/#TWIB> :

Research sponsored by drug companies is biased

<http://bmj.com/content/vol326/issue7400/twib.shtml#326/7400/0>

No more free lunches

Kamran Abbasi and Richard Smith

BMJ 2003; 326: 1155-1156.

<http://bmj.com/cgi/content/full/326/7400/1155> text

<http://bmj.com/cgi/reprint/326/7400/1155> pdf

Drug company sponsorship of education could be replaced at a fraction of its cost

<http://bmj.com/cgi/content/full/326/7400/1163> text

<http://bmj.com/cgi/reprint/326/7400/1163> pdf

Drug companies advised to publish unfavourable trial results

<http://bmj.com/cgi/content/full/326/7400/1163-a> text

<http://bmj.com/cgi/reprint/326/7400/1163-a> pdf

World body reviews doctors' links to drug industry

<http://bmj.com/cgi/content/abridged/326/7400/1165-a> abridged text

http://bmj.com/cgi/reprint_abr/326/7400/1165-a abridged pdf

<http://bmj.com/cgi/content/full/326/7400/1165-a> full text

Pharmaceutical industry sponsorship and research outcome and quality: systematic review

Joel Lexchin, Lisa A Bero, Benjamin Djulbegovic, and Otavio Clark

BMJ 2003; 326: 1167-1170.

<http://bmj.com/cgi/content/full/326/7400/1167> full text

<http://bmj.com/cgi/reprint/326/7400/1167> pdf

Evidence b(i)ased medicine—selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications

Hans Melander, Jane Ahlqvist-Rastad, Gertie Meijer, and Björn Beermann

BMJ 2003; 326: 1171-1173.

<http://bmj.com/cgi/content/full/326/7400/1171> full text

<http://bmj.com/cgi/reprint/326/7400/1171> pdf

Characteristics of general practitioners who frequently see drug industry representatives: national cross sectional study

Chris Watkins, Laurence Moore, Ian Harvey, Patricia Carthy, Elizabeth Robinson, and Richard Brawn

BMJ 2003; 326: 1178-1179.

<http://bmj.com/cgi/content/full/326/7400/1178> full text

<http://bmj.com/cgi/reprint/326/7400/1178> pdf

Who pays for the pizza? Redefining the relationships between doctors and drug companies. 1: Entanglement

Ray Moynihan

BMJ 2003; 326: 1189-1192.

<http://bmj.com/cgi/content/full/326/7400/1189> full text

<http://bmj.com/cgi/reprint/326/7400/1189> pdf

Who pays for the pizza? Redefining the relationships between doctors and drug companies. 2: Disentanglement

Ray Moynihan

BMJ 2003; 326: 1193-1196.

<http://bmj.com/cgi/content/full/326/7400/1193> full text

<http://bmj.com/cgi/reprint/326/7400/1193> pdf

How to dance with porcupines: rules and guidelines on doctors' relations with drug companies

Elizabeth Wager

BMJ 2003; 326: 1196-1198.

<http://bmj.com/cgi/content/full/326/7400/1196> full text

<http://bmj.com/cgi/reprint/326/7400/1196> pdf

How can research ethics committees protect patients better?

Silvio Garattini, Vittorio Bertele, and Luca Li Bassi

BMJ 2003; 326: 1199-1201.

<http://bmj.com/cgi/content/full/326/7400/1199> full text

<http://bmj.com/cgi/reprint/326/7400/1199> pdf

Medical journals and pharmaceutical companies: uneasy bedfellows

Richard Smith

BMJ 2003; 326: 1202-1205.

<http://bmj.com/cgi/content/full/326/7400/1202> text

<http://bmj.com/cgi/reprint/326/7400/1202> pdf

Unhealthy spin

Bob Burton and Andy Rowell

BMJ 2003; 326: 1205-1207.

<http://bmj.com/cgi/content/full/326/7400/1205> text

<http://bmj.com/cgi/reprint/326/7400/1205> pdf

Relationships between the pharmaceutical industry and patients' organisations

Andrew Herxheimer

BMJ 2003; 326: 1208-1210.

<http://bmj.com/cgi/content/full/326/7400/1208> text

<http://bmj.com/cgi/reprint/326/7400/1208> pdf

Journals should select drug advertisements more carefully

James J Oliver and Simon R Maxwell

BMJ 2003; 326: 1211. <http://bmj.com/cgi/content/full/326/7400/1211>

Charities and patient groups should declare interests

Jenny Hirst

BMJ 2003; 326: 1211.

<http://bmj.com/cgi/content/full/326/7400/1211-a>

Bioethics are difficult to balance

Asad J Raja

BMJ 2003; 326: 1215.

<http://bmj.com/cgi/content/full/326/7400/1215-c>

Then check out the astonishing articles on medical ghostwriting, starting at

<http://www.cbc.ca/consumers/market/files/health/ghostwriting/index.html>

It may inspire you to earn extra income, because it points out that a Medical Ghostwriter can make \$100,000 per year writing favorable drug reports! YMMV

Difficult to question if there is bias in drug-industry studies after reading the above.

Two recent examples of bias in the presentation of pivotal findings are:

1) Dr. Gaist's study that proves statins cause polyneuropathy <http://213.4.18.135/87.pdf>. If you read the entire research article, you will note the vast difference between his findings and the tone of the descriptive abstract, which tends to water down the findings. Further, the journal ran an editorial that provided further pro-statin spin as damage control.

2) The **ALLHAT study**, published in JAMA, was the largest to date. It ran for years and encompassed 10,000 people. Their study website <http://allhat.sph.uth.tmc.edu/default.htm> These folks were funded by NIH, and they have published what the drug companies do not want to hear: that statins do not prevent deaths. Again, there was a pro-statin damage control editorial in the same issue, and the news carriers did not highlight the findings. In fact, CNN buried it inside an article on the other finding: that diuretics worked better than other blood-pressure medications, where no reader looking for cholesterol drug results would find it.

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Glossary of some search terms & equivalents:

Lipitor = atorvastatin

Coenzyme Q10 = CoQ10 = Ubiquinone = Ubidecarenone

Statins = hydroxymethylglutaryl coenzyme A reductase inhibitors = HMG-CoA

Reductase Inhibitors

Lipitor, Mevacor, Pravachol, Zocor, Lescol, and Baycol = atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin

More to come: FAQs with published medical research on other aspects of statin adverse effects.