ATORVASTATIN vs FISH OIL

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CLINICAL RESEARCH ASSIGNMENT

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PHARMACEUTICAL PREPARATION: ATORVASTATIN

Pharmacology & Indications

The primary mechanism of action of all statins involves the inhibition of the rate-limiting enzyme in hepatic cholesterol synthesis (HMG-CoA reductase). This decrease in cholesterol production in the liver leads to increases expression of hepatic LDL receptors, resulting in a greater clearance of LDL-cholesterol from circulation *(Bryant & Knights, 2007, pg 466*

The main indications for Atorvastatin (Lipitor) are hypercholesterolemia and hyperlipidemia *(Galbraith, Bullock & Manias, 2004, pg 444)*. HMG-CoA reductase inhibitors in general are indicated for primary hypercholesterolemia (types IIa and IIb) caused by an elevated LDL-cholesterol level that cannot be controlled by diet or other treatment measures *(Bryant & Knights, 2007, pg 467)*. Lowering LDL cholesterol is said to prevent heart disease and atherosclerosis; conditions that lead to heart attack, stroke, and vascular disease. Atorvastatin has also been found to lowers elevated CRP levels, which suggests a potential anti-atherosclerotic additional benefit *(Tan et al, 2002).*

Efficacy

Manufactured by Pfizer, *Atorvastatin* amassed a staggering $10.9 billion of sales in 2004, and is amoungst the highest sold pharmaceutical items in the world *(Pfizer Inc, 2005)*. Statins are expected to reduce LDL cholesterol by up to 35%, triglyceride levels by 15% and increase HDL levels by 5% *(The Royal Australian College of General Practitioners, 2002, pg 247)* over a 4-6 month period. Broader figures indicate that statins lower total cholesterol by 10-45% and raise HDL cholesterol by 2-13% *(Bryant & Knights, 2007, pg 466)* in as little as 6 weeks. Further research reveals that HMG CoA reductase inhibitors are said to produce the greatest reduction is LDL cholesterol (30-40%) of any class of hypo-lipidemic agents *(Page et al, 1997).* In 2004, a review of 11 trials found Atorvastatin to be the gold standard for prophylaxis of cardiac ischemia and stroke *(Gresser & Gathof, 2004)*.

JAMA has reported that a reduction in CVD events has been demonstrated in patients with stable CHD as well as acute coronary syndrome patients *(Waters et al, 2002 & Schwatz et al, 2001).* However, the trail duration periods and follow-up measures are questionable. There is also evidence that there is no significant difference between Atorvastatin and placebo in the incidence of fatal cancers, serious adverse events, and liver enzyme abnormalities *(Sever et al, 2003).*

A Comparison of Cholesterol Lowering Drugs

(Adapted from NCEP Expert Panel. *JAMA*. 2001;285:2486-2497)

Drug Class	LDL-C	HDL-C	Triglycerides
Statins	18% to 60%***	5% to 15%	7% to 37%***
Bile Acid Sequestrants	15% to 30%	3% to 5%	No change
Nicotinic Acid	5% to 25%	15% to 35%	20% to 50%
Fibric Acids	5% to 20%**	10% to 20%	20% to 50%

**May be increased in patients with high triglycerides.

***Up to 60% reduction in LDL-C, and 37% reduction in triglycerides, as indicated in for Atorvastatin

In further researching, the NASDAC study concluded excellent efficacy across the dose range for all lipid parameters:

- LDL-C: -39% to -60%
- Triglycerides: -19% to -37%
- HDL-C: +5% to +9%

It should be noted that the NASDAC study was supported by a research grant from Pfizer Inc (*Jones et al, 2005)*.

Safety Issues

Overall, long-term safety data for statins is limited due to their relatively recent introduction to the market. Contraindications and cautions include *(Bryant & Knights, 2007, pg 467)*:

- Pre-existing liver / renal impairment
- Severe recurrent illness (infection, trauma)
- Organ transplant patients receiving immunosuppressant drugs
- HMG-CoA reductase sensitivities
- Pregnancy

Adverse Drug Reactions

Common adverse reactions include *(Bryant & Knights, 2007, pg 467)*:

- GIT discomfort (bloating, nausea, vomiting, flatulence, diarrhoea, indigestion, constipation, etc)
- Headaches
- Fatigue
- Rash
- Hepatotoxicity
- Myopathy, progressing to rhabdomyolysis and renal failure

Negative Interactions of Lipitor *(Sourced from Stargrove, Treasure & McKee, 2008).*

- **CoQ10;** Statins have been shown to reduce CoQ10 in individuals with hypercholesterolemia by 40-50%, with a consequent increase of ADRs (ie. Rhabdomyolysis/myopathy)
- **Gotu kola;** clinically insignificant research indicating negative interaction (*www.natural standard.com/monographs/herbssupplements/gotukola.asp*, *2001)*
- **Niacin (B_3);** Additive effect to statin therapy, although an increased incidence of side effects has also been noted with this interaction, which can lead to serious kidney problems.
- **St John's Wort;** theoretical, time dependant interaction (due to CYTP450 induction), ensure doses are separated.

- Consuming certain types of statins in conjunction with **grapefruit juice** (in large amounts) has been shown to increase blood concentrations *(Lilja et al. 2004).*
- **Beta-carotene/ Vitamin A;** increased vitamin A has been shown in one trial when taken with statins, clinical significance is unclear.
- **St Mary's Thistle;** theoretical, time dependant interaction (due to CYTP450 induction), ensure doses are separated.
- Excessive **alcohol consumption** not recommended while taking Atorvastatin as it can worsen the adverse effects of this medicine on the liver.

All statins are metabolised by the CYP450 isoform 3A4. As a result, many drugs and other substances which share this metabolic pathway can elevate plasma levels of a statin the thereby increase the risk of adverse effects such as myopathy.

Examples of classes of drugs which are also metabolised by CYP450 isoform 3A4 include: Antibiotics, antifungals, HIV-protease inhibitors, cyclosporin, fibrates & niacin. Inducers of CYP3A4 include barbiturates, carbamazepine, phenytoin & griseofulvin, which can cause a reduction in Atorvastatin plasma levels *(Bryant & Knights, 2007)*.

Cost

Minimal dosage cost would be around $1.10 p/day, and maximum dose cost would be approximately $3.50 p/day. These costs can obviously vary anywhere in between these two prices.

Dose

The initial dose is 10mg, with increased doses if need be of up to 80mg daily *(Bryant & Knights, 2007, pg 467)*. Doses are usually administered at night, as this is when cholesterol synthesis is highest. Effectiveness of the dose is determined by monitoring plasma lipid levels. After initiation and/or upon titration of Lipitor, lipid levels should be analysed within 2 to 4 weeks and dosage adjusted accordingly. The dosage of Atorvastatin must be carefully adjusted according to individual requirements, and absorption is generally enhanced by food.

For high cholesterol (oral dosage form):

- Adults: 10 - 80 mg UDS
- Children (10 to 17 years of age): 10 - 20mg UDS

COMPLEMENTARY MEDICINE ALTERNATIVE: FISH OILS

Pharmacology & Indications

The designation “omega” indicates which position the first unsaturated (double) bond occurs at the non-carboxyl end of the molecule. Three common constituents are linolenic acid, eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) *(Timberlake, 2007, pg 613)*.

Fish is the major dietary source of long-chain omega-3 PUFAs, specifically the 20 carbon EPA, and the 22 carbon DHA. Linoleic acid and linolenic acid are also essential fatty acids (EFAs). Alpha-linolenic acid (ALA) is an 18-carbon omega-3 polyunsaturated EFA that can serve as an essential precursor to both EPA and DHA. Fish oils are rapidly absorbed from the GIT and compete with arachidonic acid for incorporation into phospholipids located within cell membranes. When required, these cell membranes then release PUFAs, which are converted into 20-carbon eicosanoids, and have important and extensive physiological functions *(Braun & Cohen, 2007, pg 305)*.

Extensive research indicates that omega-3 fatty acids reduce inflammation and help prevent risk factors associated with chronic diseases such as heart disease, cancer, and arthritis. These essential fatty acids are highly concentrated in the brain and appear to be particularly important for cognitive and behavioural function *(Braun & Cohen, 2007, pg 310)*.

Efficacy

Several studies report the benefits of fish oils containing EPA (in particular) and DHA in patients with hypercholesterolemia. The *AHA (American Heart Association)* has indicated fish oils for secondary prevention in patients with CVD. As fish oils exert a wide range of different effects on the circulatory system (anti-platelet, anti-inflammatory, anti-arrhythmic, anti-thrombotic), it is suspected that the summation of these factors contribute to fish oils substantial effect on lowering morbidity and mortality associated with cardiovascular disease *(Braun & Cohen, 2007)*.

As published in *JAMA*, a groundbreaking Swiss review of 97 studies (276 115 people) found that whilst statins reduced cardiac mortality by 13% (compared to controls), Omega-3 fatty acids reduced it by a staggering 23%. Overall cardiac mortality risk reductions were 22% and 32% respectively *(Studer et al, 2005)*. A human RDCT (crossover) revealed that HDL cholesterol levels were increased by 8% when hyper-lipidemic patients were given 1480mg of DHA, and 1880mg of EPA daily for 8 weeks *(Calabresi et al, 2004)*. Clinical research has determined (in most cases) that fish oil can reduce triglyceride levels by 25-44% *(Harris, 1997 & Nenseter et al, 2000).* A prospective, double-blind, placebo-controlled trial of fourty-two patients with high triglyceride concentrations assessed the efficacy of ‘Omacor’ (a high concentrate of omega-3 fatty acids, 4 g/day for 4 months). Compared with baseline values, Omacor significantly reduced mean triglyceride concentrations by 45% ($P<0.00001$), total cholesterol by 15% ($P< 0.001$), VLDL cholesterol by 32% ($P< 0.0001$) and cholesterol: HDL cholesterol ratio by 20% ($P=0.0013$) *(Harris et al, 1985)*.

Several trials have reported slight elevation of LDL-cholesterol at lower doses, with a paradoxical lowering of LDL cholesterol at very high doses (32g/day) *(Simopoulos, 1991).* The ability of fish oils to increase LDL cholesterol levels can be negated by consuming Garlic concurrently with fish oils. Consumption of 12 grams of fish oils per day combined with 900 mg of Garlic causes an average reduction in LDL Cholesterol levels of 9.5%.

Clinical research has also clearly determined administration of Omega-3 fatty acids have the potential to reduce the burden of cardiovascular disease within society significantly. In conclusion, although fish

oils can provide a balancing effect on cholesterol ratio by modestly raising HDL, lowering VLDL and lowering triglycerides; it is incomparable to the efficacy of Atorvastatin in reducing LDL cholesterol. The therapeutic effect which fish oils exhibit seems to act through several biological mechanisms within the cardiovascular system, and not with specific cholesterol-lowering capabilities.

Safety/Adverse drug reactions

An area of growing concern is the contamination of fish oils with heavy metals (namely mercury). Fish containing methyl mercury, pesticides and other heavy metals is especially cautioned during pregnancy and lactation, and with children. Fish with higher levels of mercury include: swordfish, southern blue fin tuna, barramundi, and shark. Fish oils with lower levels of mercury include: mackerel, Atlantic salmon, herrings and sardines.

Fish oil supplementation is generally safe and well tolerated. There have been few side effects reported which include GIT discomfort, loose bowels, halitosis, and a fishy odour of the skin and urine. Caution has been advised with cod liver oil due to high content of vitamins A and D if patient has pre-existing hepatotoxic stress. Although fish oil administration carries an abundance of warnings that intake exceeding 3g/day may increase the risk of bleeding, reports of this are rare among primary clinical findings and qualified published case reports *(Stargrove, Treasure & McKee, 2008)*. However, doses of >10g p/day should be suspended 1 week before major surgery *(Braun & Cohen, 2007, pg 313)*. Patients with a known hypersensitivity to fish/seafood/nuts may react adversely. Although fish oils are indicated for those with cardiovascular disease, close monitoring (especially when at high doses) is essential.

There are many options to choose from when purchasing fish oils. All good quality fish oils have been tested for heavy metal residues before sale, be enterically coated (if capsule form), contain vitamin E (or antioxidant equivalent), be from a sustainable source, and have high levels of both DHA and EPA.

Negative Interactions with drugs/food/nutrients/herbs

- **Anti-platelets –** theoretical interaction; may increase the risk of bleeding. However one study has suggested that the combined effects may be beneficial *(Engstrom et al, 2001).*
- **Anti-coagulants –** Bleeding time is increased at doses >12g/day *(Braun & Cohen, 2007).*
- **NSAIDS –** theoretical additional anti-inflammatory effects are possible, drug dosage may need to be altered *(Braun & Cohen, 2007).*
- **Anti-Diabetic medications/nutrients/herbs -** Fish oil supplements may lower blood sugar levels a small amount. Caution is advised when using herbs, supplements or medications that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment *(Medline Plus, http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-fishoil.html, viewed on 5/10/2009).*
- **Vitamins A & D -** Cod liver oil contains the fat-soluble vitamins A and D, and therefore fish liver oil products may increase the risk of vitamin A or D toxicity *(Medline Plus, http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-fishoil.html, viewed on 5/10/2009).*
- **Ginkgo biloba –** Theoretical negative interaction due to increased bleeding times. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto *(Medline Plus, http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-fishoil.html, viewed on 5/10/2009).*
- **Antihypertensives -** Based on human studies, omega-3 fatty acids may lower blood pressure and add to the effects of drugs that may also affect blood pressure *(Medline Plus, http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-fishoil.html, viewed on 5/10/2009).*

INTEGRATIVE APPROACH

1. Fish oils (as part of integrative treatment strategy)

Fish oils and statin therapy can provide a synergistic effect in mixed lipidemias. This is especially successful when combined with a healthy diet, regular exercise, and a customised nutrient support program *(Stargrove, Treasure & McKee, 2008, pg 783)*. Most research indicates that co-administration of fish oil and statin therapy can produce a broader and more effective therapeutic effect in lowering cholesterol and triglyceride concentrations than either agent alone *(Stargrove, Treasure & McKee, 2008, pg 797)*. One study reported a significant decrease in serum triglycerides (20-30%) and in VLDL cholesterol by (30-40%) when using an EPA concentrate (2g BDS) combined with daily statin therapy (10-40mg) for one year *(Durrington et al, 2001)*.

In a double blind, randomized, placebo controlled (DBRPC) study, hyperlipidaemic patients on stable statin therapy showed that addition of omega-3-acid ethyl ester synergistically reduced triglyceride levels more than statin treatment only *(Davidson et al, 2007; Durrington et al, 2001).* A recent meta-analysis concluded that treatment with omega-3 fatty acids was a useful and safe adjunct to statin therapy *(Nambi & Ballantyne, 2006).* Fish Oils produce greater reductions in VLDL Cholesterol than statins alone *(Contacos et al, 1993)*, and EPA may increase the effectiveness of HMG-CoA Reductase Inhibitors *(Nakamura et al, 1999)*. Although fish oils do not specifically reduce the adverse drug reactions, they increase the efficacy of statins significantly, decrease the drug requirement and considerably reduce CVD incidence.

The safety profile of fish oils has been discussed earlier.

2. Coenzyme Q10

Statin-induced CoQ10 deficiency is entirely preventable with supplemental CoQ10, with no adverse impact in the cholesterol lowering or anti-inflammatory properties of statins *(Langsjoen & Langsjoen, 2003)*. Statins have been shown to reduce CoQ10 in individuals with hypercholesterolemia by as much as 40-50%. A recent clinical trial of 32 subjects using statin treatment were either given 100 mg CoQ10/day or Vitamin E. 16 out 18 patients in the CoQ10 group reported improvements. In average CoQ10 subjects showed a decrease of 40 % of pain severity and 38% pain interference. No change was evident in the control group. *(Caso et al, 2007).*

A systematic review of over 34 controlled studies concluded that CoQ10 supplementation goes beyond correction of a deficiency state, with strong evidence suggesting it has the potential to reduce the overall risk of CVD in its own right *(Langsjoen et al, 1999)*. Doses between 50-300mg/day have been used in CVD with no significant side-effects. Concomitant administration of CoQ10 during statin therapy offers the opportunity to derive benefits from statins, whilst counteracting some of their more serious adverse effects (ie. Rhabdomyolysis/Myopathy) and supporting broader clinical outcomes. In my opinion, co-administration of Atorvastatin and CoQ10 is essential.

Safety: All available evidence suggests that CoQ10 is generally safe, even at high doses. It has an excellent safety profile when combined with both statins and other herbs/nutrients, with no contraindications or precautions *(Stargrove, Treasure & McKee, 2008)*.

3. Garlic

Garlic is inexpensive, safe, and a beneficial adjunct to Atorvastatin. Concomitant administration of garlic may provide a synergistic effect in lowering triglycerides while preventing any moderate fish oil-induced rise in LDL cholesterol *(Alder & Holub, 1997)*. Co-administration of garlic with statins may

enable lower statin drug doses, and therefore a reduced risk of drug-induced adverse effects *(Stargrove, Treasure & McKee, 2008, 55)*. As previously mentioned, consumption of 12 grams of fish oils per day combined with 900 mg of Garlic causes an average reduction in LDL Cholesterol levels of 9.5%. The evidence points to fresh garlic as an effective complimentary medicine for lowering blood cholesterol. Garlic enhances the efficacy of statins, and like fish oils, considerably lessens the overall disease process.

Safety/Interactions: Caution with anti-platelet medications. Cessation of high dose garlic consumption is recommended before surgery, however based on current evidence, the risk of garlic-induced bleeding the interactions with other drugs affecting haemostasis appears to be very low *(Macan et al, 2006)*.

4. Phytosterols

Phytosterols (plant sterols) are cholesterol-like molecules found primarily in vegetable oils. Present evidence is sufficient to promote use of sterols for lowering LDL cholesterol levels in persons at increased risk for coronary heart disease *(Katan et al, 2003)*.

Recently, investigators reported that phytosterol intake of 2-3 g/day can reduce LDL cholesterol levels of about 7-11% in human subjects *(Lugasi, 2009)*. A number of other trial have suggested that intake of 1.5-2.0 g/day of phytosterols can result in a 10-15% reduction in LDL cholesterol in as short as a 3-week period in hyperlipidemic populations. Added benefits of phytosterol consumption have been demonstrated in people who are already on statin therapy *(Micallef & Garg, 2009)*. A major Australian study of 152 patients found that adding sterols to margarine lowered LDL a further 8% in patients on statins, with the addition of sterol-ester margarine to statin therapy offering LDL cholesterol reduction equivalent to doubling the dose of statin *(Simons, 2002)*.

Safety: The FSANZ states that human studies did not provide any evidence of adverse effects associated with consumption of table spreads containing phytosterols. *(FSANZ, http://www.foodstandards.gov.au/standardsdevelopment/applications/applicationa410phytosterolesters/applicationa410fulla991.cfm, viewed on 5/10/2009).*

5. Fibre (Psyllium/Oats)

Psyllium is a well tolerated, safe and useful adjunct to diet therapy for those with mild-moderate hypercholesterolaemia. A meta-analysis of 8 RCTs showed that 10.2g of psyllium/day with a low-fat diet lowered total cholesterol by 4% and LDL by 7% *(Anderson et al, 2000).* A recent randomised trail compared the efficacy and safety of Isapgol (psyllium husks) plus Atorvastatin versus Atorvastatin alone. After 12 weeks the fall in LDL-C at 31.4% for Isapgol + Atorvastatin was significantly greater than 22.8% among the Atorvastatin group ($p < 0.05$) *(Jayram et al, 2007).* Another study showed that a 10mg statin plus psyllium could achieve similar efficacy as 20 mg statin treatment *(Moreyra et al, 2005)*. With pysllium alone, a cholesterol lowering effect is to be expected after approximately 8 weeks *(Braun & Cohen, 2007),* when used in conjunction with dietary parameters. Oat bran contains beta-glucans that are known for sequestering bile acids. Oat bran has been shown to reduce LDL cholesterol by up to 16% *(Davidson et al, 1991)*, with the addition of oat milk having a further 6% reduction *(Onning et al, 1999)*. Oatbran and oatbased cereals can reduce cholesterol levels within 5-6 weeks *(Stargrove, Treasure & McKee, 2008, pg 497)*. Overall, fibre decreases the drug requirement (and therefore decreases adverse drugs effects), lessens the overall disease process, and significantly increases the efficacy of Atorvastatin.

Safety/Interactions: Bloating and flatulence are common complaints *(Behall et al, 2002).* Dietary oats should be avoided in cases of intestinal obstruction and coeliac disease *(Braun & Cohen, 2007, pg 497).* Co-administration of psyllium and many medications/nutrients/herbs can lead decreased drug absorption. Separate doses by 1-3 hours.

Interactions with other food/nutrients/herbs

Other beneficial/synergistic interactions of natural medicines with Atorvastatin:

1. **Carnitine;** positive/beneficial interaction in lowering lipoprotein (a) levels *(Sirtori et al, 2000)*
2. **Vitamin C & Selenium**; potentially positive interaction (due to antioxidant activity)
3. **Reishi;** theoretical positive interaction
4. **Policosanol;** Clinically significant or synergistic effect is possible, however research finding are mixed and further investigative studies are required. Concomitant use has much potential to increase efficacy of statin, and enable a reduced dosage, therefore lowering adverse effects *(Stargrove, Treasure & McKee, 2008, pg 809)*.
5. **Red Rice Yeast;** Co-administration could potentially be beneficial leading to reduced doses of statins; more research is required in this area.
6. **Niacin (vitamin B3)**; Although niacin has well established benefits, the side effects can be still quite substantial, and co-administration should be closely monitored.
7. **Probiotics;** Possible strain dependant beneficial interaction, further research needed *(Liong, 2007)*
8. **Cynara scolymus;** Cynara has hepatoprotective, hepatotrophorestorative, cholaretic, cholagogue, bitter tonic and hypocholesterolemia actions. Clinical data from uncontrolled trials (1936 to 1994) showed a capacity to reduce cholesterol/triglyceride levels in a range from 5% to 45% *(Bone, 2003, pg 243).*

CONCLUSION: TREATMENT STRATEGY

The additive effects of these cholesterol-lowering treatments with Atorvastatin significantly increase the efficacy of the drug. This may allow for a reduced dose, which would considerably contribute to a decrease in adverse drug effects. Furthermore, these complementary medicines all delay and can even reverse the entire disease process in their own right.

Nutrient/Herb	Dose
Fish oil liquid	5mL TDS
Coenzyme Q10 (150mg)	1 capsule BDS with food
Psyllium	2 teaspoons UDS(with water)
Oats with oat milk	Dietary inclusion (30g at breakfast)
Cynara scolymus (LE)	10mL UDS before retiring
Phytosterols (rice bran/wheat germ/ flaxseed oil)	Dietary inclusion
Garlic (fresh raw crushed)	5 grams (2-3 cloves) daily

Dietary and Lifestyle measures:

Dietary and lifestyle changes are essential for reducing your risk of cardiovascular disease. They may have a greater impact on reducing the morbidity and mortality risk of heart disease than medication alone. Specific lifestyle suggestions that will improve cholesterol, and most all of the other risk factors for heart disease include:

- Quit smoking
- Regular exercise
- Stress reduction
- Moderate/low alcohol intake
- Eat a healthy diet rich in vegetables, fruit, fibre, nuts/seeds and antioxidants. Reduce intake of trans-fats/hydrogenated products, salt, refined sugars, and processed goods. Ensure adequate protein levels are met, and replace trans/saturated fats with essential fatty acids where possible.

Expected Outcome:

For patients with hypercholesterolaemia (particularly secondary to diet/disease/medication/lifestyle), there are a range of herbs and nutrients which can have a profound effect on overall cholesterol reduction. This is especially the case if an integrative plan (as above) is adopted and compliance is upheld. With this integrative plan, a reduction in cholesterol levels would be expected within 6 weeks, with efficacy increasing over time. Complications of dietary/complementary medicine as a lone agent (ie. without statins) in reducing cholesterol include cost, high doses (ie. fish oils/ garlic), and poor compliance due to long term treatment protocols and dietary inclusions.

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