EFFECTS OF FLUOXETINE WITH AND WITHOUT OMEGA-3 FATTY ACID EICOSAPENTAENOIC ACID ON CARDIOVASCULAR DISEASE RISK IN DEPRESSIVE PATIENTS

Shima Djazayeri[(1)], Seyed Ali Keshavarz[(2)], Mehdi Tehrani-Doost[(3)], Mostafa Hosseini[(4)], Mahmoud Jalali[(5)], Homayoun Amini[(6)], Maryam Chamari[(7)], Abolghassem Djazayery[(8)]

Abstract

INTRODUCTION: Depression seems to be an independent risk factor for cardiovascular disease (CVD). Little is known about the effects of treatment of depression on CAD risk factors. The objective of this study was to determine whether cardiac risk is altered following 8 weeks of treatment of depression with fluoxetine. A secondary aim was to examine whether an omega-3 fatty acid eicosapentaenoic acid (EPA) plus fluoxetine affected the change in CAD risk compared with fluoxetine alone.

METHODS: Forty patients with a diagnosis of major depression were randomly allocated to receive daily 20 mg fluoxetine plus either 1 g EPA or its placebo for 8 weeks. The 24-item Hamilton Rating Scale for Depression (a validated scoring system usually used in studies of antidepressant medication) was utilized to evaluate clinical symptoms of patients. Cardiac risk was estimated using fasting plasma or serum levels of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol LDL-C, cortisol and C-reactive protein (CRP) at baseline and at week 8.

RESULTS: Depression severity was decreased significantly in both groups. CRP and cortisol decreased significantly after treatment. EPA plus fluoxetine did not affect the change in CRP and cortisol compared to fluoxetine alone. Total cholesterol did not change significantly after 8 weeks of treatment. LDL-C/HDL-C ratio increased after treatment without difference between treatment groups.

CONCLUSIONS: Treatment of patients with major depression by fluoxetine with or without EPA could lower CAD risk due to decreases in cortisol and CRP. Although LDL to HDL ratio increased, its importance in CAD risk is not clear, as LDL size and HDL subclasses were not measured in this study. EPA plus fluoxetine did not have any significant effect on the change of these risk factors compared to fluoxetine alone in this 8-week trial.

Keywords: cardiovascular disease risk, depression, fluoxetine, omega-3.

***ARYA Atherosclerosis Journal* 2007, 3(3): 151-156**

Date of submission: 25 Aug 2007, ***Date of acceptance:*** 11 Nov 2007

Introduction

Depression seems to be an independent risk factor for cardiovascular disease (CVD).[1, 2] Several mechanisms have been suggested for this relation.[3] One mechanism is that depression is accompanied by

1) MD, PhD student, Department of Nutrition and Biochemistry, School of Public Health, Tehran University of Medical Sciences (TUMS), Tehran, Iran.
2) Professor, Department of Nutrition and Biochemistry, School of Public Health, TUMS, Tehran, Iran. P.O. Box 14155-6446 Tehran, Iran. Phone: 88954924. Fax: 88974462. Email: s_akeshavarz@yahoo.com
3) MD. Assistant professor, Roozbeh Hospital, Department of Psychiatry, School of Medicine, TUMS, Tehran, Iran.
4) MD, Associate professor, Department of Epidemiology and Biostatistics, School of Public Health, TUMS, Tehran, Iran.
5) MD, Professor, Department of Nutrition and Biochemistry, School of Public Health, TUMS, Tehran, Iran.
6) MD, Associate professor, Roozbeh Hospital, Department of Psychiatry, School of Medicine, TUMS, Tehran, Iran.
7) BS, Department of Nutrition and Biochemistry, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.
8) PhD, Professor, Department of Nutrition and Biochemistry, School of Public Health, TUMS, Tehran, Iran.

Corresponding author: Seyed Ali Keshavarz

activation of the inflammatory system.[4,5] Case-control studies have shown that inflammatory markers such as C-reactive protein (CRP) are elevated in depression.[6] CRP is an independent risk factor for coronary heart disease.[7] An alternative mechanism is that major depression is associated with altered changes in hypothalamo-pituitary-adrenocortical (HPA) activity.[8] Hypercortisolemia is associated with metabolic syndrome in depression.[9] Little is known about the effects of treatment of depression on CAD risk factors.[10] Fluoxetine is a selective serotonin reuptake inhibitor which is commonly used in treatment of depression. The objective of this study was to determine whether CVD risk is altered following 8 weeks of treatment of depression with fluoxetine. A secondary aim was to examine whether eicosapentaenoic acid (EPA) plus fluoxetine affected the change in CAD risk compared with fluoxetine alone. EPA is an omega-3 fatty acid. Long chain cmega-3 fatty acids have been shown to be cardioprotective[11]. However, different omega-3 fatty acids have different effects on lipid profile.[12]

Materials and methods

Forty patients with major depression were referred from Roozbeh Psychiatry Hospital, Tehran University of Medical Sciences to participate in the study. All the patients signed the informed consent. The protocol was approved by the Research Ethics Committee of Tehran University of Medical Sciences.

The patients met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for major depressive disorder without psychotic features based on the clinical interview. They did not receive any medication for at least 6 weeks. The exclusion criteria were comorbid psychiatric diagnosis other than dysthymia and anxiety, medical illness established by medical history, physical examination or laboratory tests, suicidal thoughts, substance abuse, pregnancy and lactation, consumption of ω-3 FA supplements in the previous year, and dietary intake of more than one serving of fish per week.

Patients were randomly allocated to receive daily 20 mg fluoxetine plus either 1 g EPA or its placebo for 8 weeks. The study was double blind. The 24-item Hamilton Rating Scale for Depression (a validated scoring system usually used in studies of antidepressant medication) was utilized to determine depression severity and evaluate clinical symptoms of patients at baseline and after 8 weeks of treatment. Cardiac risk was estimated using plasma or serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), cortisol and CRP. Blood samples were obtained after 12-14 hours of fasting at baseline and after 8 weeks of treatment. Plasma and serum was isolated and frozen at -70 ˚C until analyzed. TC, HDL-C and LDL-C were measured using a Hitachi autoanalyzer (Bochringer, Mannheim, Indianpolis, IN) by commercially available enzymatic kits (Pars Azmoon, Tehran, Iran). CRP was measured with a particle-enhanced immuno-turbidimetry using commercially available enzymatic kits (Pars Azmoon, Tehran, Iran). Cortisol was measured by radioimmunoassay with the commercially available kits (Immunotech, Canada).

Statistical analysis was performed using SPSS (version 13). Data were described as the mean ± SD for TC, HDL-C and LDL-C and cortisol which have a normal distribution. Since the distribution of CRP was skewed, its logarithm was used in the analysis. Changes in TC, HDL-C, LDL-C, CRP and cortisol were analyzed by using two-way (time and treatment group) analysis of variance. A significance level of 0.05 was used to determine the statistical significance.

Results

A total of 40 patients were recruited to the study (20 in each group). Twenty-eight patients (14 patients in each group) aged 35.4±9.7 years old, 64% female, with a body weight of 70.85±14.04 kg (BMI= 26.94±7.17 kg/m²) completed 8 weeks of the study and had biochemical measurements, so they were included in the analysis. Severity of depression decreased significantly in both groups from 29.93±6.18 to 14.07±6.16 scores (P<0.001). CRP and cortisol decreased significantly after treatment. EPA plus fluoxetine did not affect the change in CRP and cortisol compared to fluoxetine alone.

Body mass index (BMI) decreased significantly after treatment in fluoxetine group (P=0.006) but not in the EPA plus fluoxetine group (P= 0.44). LDL-C/HDL-C ratio increased after treatment (P=0.01) with no difference between treatment groups (P=0.63).

TABEL 1. Cardiovascular risk factors before and after 8 weeks of treatment of depression§

				Time		Time and group interaction	
	study group	Week 0	Week 8	F	P value	F	P value
Cortisol (mM/l)			113.71 ± 39.28 101.57 ± 40.42	7.585	0.011*	1.253	0.273
log CRP			-0.38 ± 0.23 -0.22 ± .040	14.092	0.001*	0.008	0.929
TC † (mg/dl)			191.00 ± 36.63 182.71 ± 33.03	0.328	0.571	4.344	0.047**
HDL-C‡ (mg/dl)			44.79 ± 7.84 52.85 ± 11.79	3.875	0.060	2.934	0.099
LDL-C¶ (mg/dl)	fluoxetine Fluoxetine+EPA	97.07 ± 30.22 86.93 ± 18.43	101.43 ± 24.10 96.57 ± 25.17	2.968	0.097	0.423	0.521

§Two-way (time and treatment group) repeated-measure analysis of variance was used
*The change after 8 weeks is significant
**The change in TC was different among groups
†Total cholesterol
‡High-density lipoprotein cholesterol
Low-density lipoprotein cholesterol

Discussion

Fasting serum cortisol decreased significantly after 8 weeks of treatment. This finding is in line with most previous studies which have reported that cortisol levels or HPA activation decreases after treatment of depression.[13-17] However, Kaufman and associates[18] and Marques-Deak[19] and associates reported that after 8 weeks of treatment with citalopram (a selective serotonin reuptake inhibitor which is used for treatment of depression), cortisol levels did not change. As major depression is associated with overactivity of HPA,[8] we expect the treatment to normalize activation of this axis, but other factors such as hospitalization stress and treatment duration may influence its levels. Stress can increase HPA activity.[20] In our study, all patients were outpatients. Cortisol decrease could potentially reduce the risk of CAD as it is associated with insulin resistance and abdominal obesity.[3,9] EPA plus fluoxetine did not affect the change in cortisol levels versus fluoxetine alone. This finding is consistent with a previous studies showing that omega-3 fatty acids could not decrease cortisol concentration in severely ill patients after 4 days.[21]

CRP decreased significantly after 8 weeks of treatment. Previous studies have reported inconsistent findings about CRP levels after treatment of depression. Dawood and associates[22] reported increased CRP levels and Yanic and associates[23] found no change in cortisol levels after treatment. Our finding are comparable to Tuglu and associates[24] showing a decrease in CRP levels after treatment. As depression is associated with an inflammatory response,[8] we expect resolution of depression to lead to a reduction of CRP levels. These discrepancies result from methods of CRP assessment and hospitalization stress. Stress can raise the activity of immune system.[20] As CRP level can predict future CAD risk,[7] its decrease could potentially decrease atherosclerosis and risk of CAD.[25] EPA plus fluoxetine did not affect the change in CRP compared to fluoxetine. This is in the line with a previous study reporting that 4 weeks of omega-3 supplementation had no effect on CRP levels in healthy subjects and CAD patients.[26]

HDL-C had a tendency to decrease after treatment, although it was not significant. Previous studies on the effects of treatment of depression on HDL-C levels are rather scarce. Maes and associates[27] reported no change in HDL-C cholesterol after 5 weeks of treatment with antidepressants, while Kopf and associates[13] observed significant increase in HDL-C after 35 days of treatment with antidepressants. Evidence suggests that there is a genetic predisposition to both major depressive disorder and imbalances in HDL-C metabolism in some people. A variation of

chromosome 16 may predispose patients, both to major depression and lecithine cholesterol acyl transferase (LCAT) enzyme deficiency;[28] this enzyme decreases HDL-C. The imbalances in HDL-C metabolism might account for the HDL-C decrease in our study. Hospitalization and compliance with hospital diet and physical activity may have led to improvements in HDL-C in the previous study. Addition of EPA to fluoxetine had a tendency to compensate HDL-C decrease although it was not significant. Previous studies have shown that omega-3 fatty acids can increase HDL-C and HDL2-C.[29, 30] HDL2-C correlates inversely with CAD.[31]

The increase in LDL-C was not statistically significant. Kopf and associates[13] reported increased LDL-C levels after 35 days of treatment with amitriptyline or paroxetine. In another study there was an 0.8 mg increase in LDL-C in patients treated with fluoxetine for eight weeks.[32] It has been reported that serum IL-6 concentration in patients with major depressive disorder tends to be higher than in normal controls and decreases significantly after treatment.[33, 34] IL-6 increases LDL receptors in the liver.[35] Treatment of depression leads to a decrease in IL-6 levels and thus a to a decrease in LDL receptors and an increase in serum LDL-C levels. Furthermore, serum cortisol decreased in our study. Cortisol has a direct influence on lipid metabolism in the liver. It inhibits VLDL synthesis in the liver by induction of peroxisome proliferating activator receptor (PPAR)[36] leading to decreased serum LDL-C. Therefore a longer treatment duration might have led to a significant increase in LDL-C, but the risk of CAD does not necessarily increase as reported by Kopf and associates.[13] Although LDL-C had increased after 35 days of treatment with antidepressants, triglyceride levels (which indicate LDL atherogenecity[37]) decreased . We did not measure LDL-triglyceride in this study. EPA plus fluoxetine had no effect on the LDL-C change versus fluoxetine. EPA alone has been reported to have no effect on LDL-C.[38]

Total cholesterol did not change after 8 weeks of treatment of depression. This finding was consistent with a study of 8 weeks of treatment with citalopram in which cholesterol levels did not change in women of reproductive age,[18] but two other studies reported an increase in cholesterol levels following treatment of depression with antidepressants other than fluoxetine.[28,39] Furthermore, Caycoylu and associates found a decrease in cholesterol levels after 6 weeks of treatment with antidepressants.[10] It has been suggested that weight increase after treatment with antidepressants may mediate the adverse changes in cholesterol levels.[40] In hospitalized patients, compliance with hospital food and physical activity may help decrease cholesterol levels. In our study, body weight of the patients did not increase. TC change was different between treatment groups. BMI decreased significantly in the fluoxetine group but not in the combined group, thus it had effects on TC.

In conclusion, treatment of patients with major depression by fluoxetine with or without EPA could lower CAD risk due to decreases in cortisol and CRP. Although LDL-C to HDL-C ratio increased, its importance in CAD risk is not clear, as LDL size and HDL-C subclasses were not measured in this study. EPA plus fluoxetine did not have any significant effect on the change of these risk factors compared to fluoxetine alone. Further studies with more patients and longer duration and measurement of small-dense LDL and HDL-C subclasses are warranted to determine the effects of treatment of fluoxetine with and without EPA on CAD risk.

Acknowledgements

This work was supported by Vice-Chancellery for Research, Tehran University of Medical Sciences. Thanks are extended to Minami Nutrition, Belgium for supplying us with plusEPA soft gels. We also acknowledge the cooperation and help of Dr. V. Sharifi, Dr. E. Izadian, and Dr. M. Arbabi.

Reference

1. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: Systematic review and meta analysis. *International Journal of Geriatric Psychiatry*. 2007;22:613-626.
2. Massart N, Triffaux JM. [Depression and coronary artery disease]. *Rev Med Liege*. 2005;60:931-938.
3. Lett HS, Blumenthal JA, Babyak MA, Sherwoob A, Strauman T, Robins C, Newman MF. Depression as a risk factor for coronary artery disease: Evidence, mechanisms, and treatment. *Psychosomatic Medicine*. 2004;66:305-315.
4. Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29:201-217.
5. Schlatter J, Ortun?o F, Pla J, Cervera-Enguix S. Parameters of natural immunity as biological markers of depression. *Parame?tros de inmunidad natural como marcadores biolo?gicos de la depresio?n*. 2006;13:158-166.
6. De Berardis D, Campanella D, Gambi F, La Rovere R, Carano A, Conti CM, Silvestrini C, Serroni N, Piersanti D, Di Giuseppe B, Moschetta FS, Cotellessa C, Fulcheri M, Salerno RM, Ferro FM. The role of C-reactive protein in mood disorders. *International Journal of Immunopathology and Pharmacology*. 2006;19:721-725.
7. Inoue N. Vascular C-reactive protein in the pathogenesis of coronary artery disease: Role of vascular inflammation and oxid-

ative stress. *Cardiovascular and Hematological Disorders - Drug Targets*. 2006;6:227-231.
8. Huang T, Chen J. Cholesterol And Lipids In Depression: Stress, Hypothalamo-Pituitary-Adrenocortical Axis, And Inflammation/Immunity. In: Makowski GS, ed. *Advances in Clinical Chemistry*; 2005.
9. Vogelzangs N, Suthers K, Ferrucci L, Simonsick EM, Ble A, Schrager M, Bandinelli S, Lauretani F, Giannelli SV, Penninx BW. Hypercortisolemic depression is associated with the metabolic syndrome in late-life. *Psychoneuroendocrinology*. 2007;32:151-159.
10. Caykoylu A, Kuloglu M, Gecici O, Coskun I, Kirpinar I. The effects of antidepressant treatment on serum cholesterol and triglyceride levels in depressive patients. *Neurology Psychiatry and Brain Research*. 2007;14:13-18.
11. Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, Worthington HV, Durrington PN, Higgins JPT, Capps NE, Riemersma RA, Ebrahim SBJ, Smith GD. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: Systematic review. *British Medical Journal*. 2006;332:752-755.
12. Anil E. The impact of EPA and DHA on blood lipids and lipoprotein metabolism: influence of apoE genotype. *Proc Nutr Soc*. 2007;66:60-68.
13. Kopf D, Westphal S, Luley CW, Ritter S, Gilles M, Weber-Hamann B, Lederbogen F, Lehnert H, Henn FA, Heuser I, Deuschle M. Lipid metabolism and insulin resistance in depressed patients: Significance of weight, hypercortisolism, and antidepressant treatment. *Journal of Clinical Psychopharmacology*. 2004;24:527-531.
14. Nikisch G, Mathe AA, Czernik A, Thiele J, Bohner J, Eap CB, Agren H, Baumann P. Long-term citalopram administration reduces responsiveness of HPA axis in patients with major depression: relationship with S-citalopram concentrations in plasma and cerebrospinal fluid (CSF) and clinical response. *Psychopharmacology (Berl)*. 2005;181:751-760.
15. Schule C, Baghai TC, Eser D, Zwanzger P, Jordan M, Buechs R, Rupprecht R. Time course of hypothalamic-pituitary-adrenocortical axis activity during treatment with reboxetine and mirtazapine in depressed patients. *Psychopharmacology (Berl)*. 2006;186:601-611.
16. Navines R, Martin-Santos R, Gomez-Gil E, Martinez de Osaba MJ, Imaz ML, Gasto C. Effects of citalopram treatment on hypothermic and hormonal responses to the 5-HT1A receptor agonist buspirone in patients with major depression and therapeutic response. *Psychoneuroendocrinology*. 2007;32:411-416.
17. Inder WJ, Prickett TC, Mulder RT, Donald RA, Joyce PR. Reduction in basal afternoon plasma ACTH during early treatment of depression with fluoxetine. *Psychopharmacology (Berl)*. 2001;156:73-78.
18. Kauffman RP, Castracane VD, White DL, Baldock SD, Owens R. Impact of the selective serotonin reuptake inhibitor citalopram on insulin sensitivity, leptin and basal cortisol secretion in depressed and non-depressed euglycemic women of reproductive age. *Gynecological Endocrinology*. 2005;21:129-137.
19. Marques-Deak AH, Neto FL, Dominguez WV, Solis AC, Kurcgant D, Sato F, Ross JM, Prado EB. Cytokine profiles in women with different subtypes of major depressive disorder. *J Psychiatr Res*. 2007;41:152-159.
20. Leonard BE. HPA and immune axes in stress: Involvement of the serotonergic system. *NeuroImmunoModulation*. 2006;13:268-276.
21. Tappy L, Berger MM, Schwarz JM, Schneiter P, Kim S, Revelly JP, Chiolero R. Metabolic effects of parenteral nutrition enriched with n-3 polyunsaturated fatty acids in critically ill patients. *Clin Nutr*. 2006;25:588-595.
22. Dawood T, Lambert EA, Barton DA, Laude D, Elghozi JL, Esler MD, Haikerwal D, Kaye DM, Hotchkin EJ, Lambert GW. Specific serotonin reuptake inhibition in major depressive disorder adversely affects novel markers of cardiac risk. *Hypertens Res*. 2007;30:285-293.
23. Yanik M, Erel O, Altindag A, Kati M. The relationship between high sensitive C-Reactive protein levels and treatment response in patients with major depression. *Majo?r depresyonda hassas c-Reaktif protein du?zeyleri ve tedavi ile i?lis?kisi*. 2004;14:9-13.
24. Tuglu C, Kara SH, Caliyurt O, Vardar E, Abay E. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. *Psychopharmacology (Berl)*. 2003;170:429-433.
25. Aukrust P, Yndestad A, Smith C, Ueland T, Gullestad L, Damas JK. Chemokines in cardiovascular risk prediction. *Thromb Haemost*. 2007;97:748-754.
26. Burns T, Maciejewski SR, Hamilton WR, Zheng M, Mooss AN, Hilleman DE. Effect of omega-3 fatty acid supplementation on the arachidonic acid:eicosapentaenoic acid ratio. *Pharmacotherapy*. 2007;27:633-638.
27. Maes M, Smith R, Christophe A, Vandoolaeghe E, Van Gastel A, Neels H, Demedts P, Wauters A, Meltzer HY. Lower serum high-density lipoprotein cholesterol (HDL-C) in major depression and in depressed men with serious suicidal attempts: Relationship with immune-inflammatory markers. *Acta Psychiatrica Scandinavica*. 1997;95:212-221.
28. Gabriel A. Changes in plasma cholesterol in mood disorder patients: Does treatment make a difference? *Journal of Affective Disorders*. 2007;99:273-278.
29. Rose EL, Holub BJ. Effects of a liquid egg product containing fish oil on selected cardiovascular disease risk factors: A randomized crossover trial. *Food Research International*. 2006;39:910-916.
30. Woodman RJ, Mori TA, Burke V, Puddey IB, Watts GF, Beilin LJ. Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension. *American Journal of Clinical Nutrition*. 2002;76:1007-1015.
31. Phan BAP, Chu B, Polissar N, Hatsukami TS, Yuan C, Zhao XQ. Association of high-density lipoprotein levels and carotid atherosclerotic plaque characteristics by magnetic resonance imaging. *International Journal of Cardiovascular Imaging*. 2007;23:337-342.
32. Thase ME, Corya SA, Osuntokun O, Case M, Henley DB, Sanger TM, Watson SB, Dube S. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2007;68:224-236.
33. Kim YK, Na KS, Shin KH, Jung HY, Choi SH, Kim JB. Cytokine imbalance in the pathophysiology of major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2007;31:1044-1053.
34. Yasui T, Maegawa M, Tomita J, Miyatani Y, Yamada M, Uemura H, Ueno Si, Numata S, Ohmori T, Tsuchiya N, Yuzurihara M, Takeda S, Irahara M. Association of serum cytokine concentrations with psychological symptoms in midlife women. *Journal of Reproductive Immunology*. 2007;75:56-62.
35. Colwell Vanni HE, Gordon BR, Levine DM, Sloan BJ, Stein DR, Yurt RW, Saal SD, Parker TS. Cholesterol and interkeukin-6 concentrations relate to outcomes in burn-injured patients. *Journal of Burn Care and Rehabilitation*. 2003;24:133-141.
36. Vidal-Puig AJ, Considine RV, Jimenez-Lin?an M, Werman A, Pories WJ, Caro JF, Flier JS. Peroxisome proliferator-activated receptor gene expression in human tissues: Effects of obesity,

weight loss, and regulation by insulin and glucocorticoids. *Journal of Clinical Investigation.* 1997;99:2416-2422.
37. Deckelbaum RJ, Galeano NF. Small dense low density lipoprotein: Formation and potential mechanisms for atherogenecity. *Israel Journal of Medical Sciences.* 1996;32:464-468.
38. Cazzola R, Russo-Volpe S, Miles EA, Rees D, Banerjee T, Roynette CE, Wells SJ, Goua M, Wahle KWJ, Calder PC, Cestaro B. Age- and dose-dependent effects of an eicosapentaenoic acid-rich oil on cardiovascular risk factors in healthy male subjects. *Atherosclerosis.* 2007;193:159-167.
39. Roessner V, Demling J, Bleich S. Doxepin Increases Serum Cholesterol Levels. *Canadian Journal of Psychiatry.* 2004;49:74-75.
40. McIntyre RS, Soczynka JK, Konarski JZ, Kennedy SH. The effect of antidepressants on lipid homeostasis: A cardiac safety concern? *Expert Opinion on Drug Safety.* 2006;5:523-537.