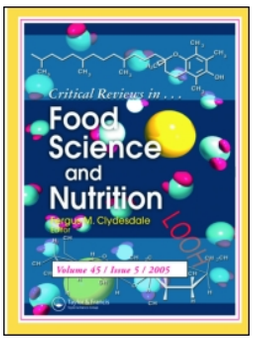

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

Omega 3 polyunsaturated fatty acids and the treatment of depression

Gelinda Deacon, Christine Kettle, David Hayes, Christina Dennis & Joseph Tucci

To cite this article: Gelinda Deacon, Christine Kettle, David Hayes, Christina Dennis & Joseph Tucci (2017) Omega 3 polyunsaturated fatty acids and the treatment of depression, Critical Reviews in Food Science and Nutrition, 57:1, 212-223, DOI: 10.1080/10408398.2013.876959

To link to this article: http://dx.doi.org/10.1080/10408398.2013.876959

Accepted author version posted online: 01 Apr 2015.
Published online: 01 Apr 2015.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
2017, VOL. 57, NO. 1, 212–223
http://dx.doi.org/10.1080/10408398.2013.876959

Taylor & Francis
Taylor & Francis Group

Omega 3 polyunsaturated fatty acids and the treatment of depression

Gelinda Deacon[a], Christine Kettle[a], David Hayes[b], Christina Dennis[b], and Joseph Tucci[b]

[a]Pharmacy and Applied Science, La Trobe University, Victoria, Australia; [b]School of Pharmacy, La Trobe University, Victoria, Australia

ABSTRACT

Depression is a common, recurrent, and debilitating illness that has become more prevalent over the past 100 years. This report reviews the etiology and pathophysiology of depression, and explores the role of omega 3 polyunsaturated fatty acids (n-3 PUFA) as a possible treatment. In seeking to understand depression, genetic factors and environmental influences have been extensively investigated. Research has led to several hypotheses for the pathophysiological basis of depression but a definitive pathogenic mechanism, or group thereof, has hitherto remained equivocal. To date, treatment has been based on the monoamine hypothesis and hence, selective serotonin reuptake inhibitors have been the most widely used class of medication. In the last decade, there has been considerable interest in n-3 PUFAs and their role in depression. These fatty acids are critical for development and function of the central nervous system. Increasing evidence from epidemiological, laboratory, and randomized placebo-controlled trials suggests deficiency of dietary n-3 PUFAs may contribute to development of mood disorders, and supplementation with n-3 PUFAs may provide a new treatment option. Conclusions based on systematic reviews and meta-analyses of published trials to date vary. Research into the effects of n-3 PUFAs on depressed mood is limited. Furthermore, results from such have led to conflicting conclusions regarding the efficacy of n-3 PUFAs in affecting reduction in symptoms of depression. PUFAs are generally well tolerated by adults and children although mild gastrointestinal effects are reported. There is mounting evidence to suggest that n-3 PUFAs play a role in depression and deserve greater research efforts.

KEYWORDS

Arachidonic acid; adrenocorticotrophic hormone; alpha-linolenic acid; brain-derived neurotrophic factor; interleukin-1β; monoamine oxidase inhibitors; serotonin; noradrenaline; positron emission tomography; mood disorder

Introduction

Depression is a universal illness affecting people of all races, societies, and age. The World Health Organization estimates that depression affects approximately 350 million people worldwide, is becoming more common, and is the leading cause of disability (WHO, 2012).

Depression is part of a group of mental and behavioral problems termed "affective" or mood disorders. The world Mental Health Survey, which was a study across 17 countries, reported that 5% of people surveyed experienced an episode of depression in the previous 12 months (WHO, 2012). In the 2007 Australian Bureau of Statistics National Survey of Health and Wellbeing, approximately 995,900 Australians (aged between 18 and 65 years) were reported as having an affective disorder diagnosed, according to the WHOs ICD 10th Revision for classification of diseases, within the 12 months prior to the survey (ABS, 2007). A similar survey conducted in 1997 found approximately 778,000 Australian adults (aged 16 years and over) were classified as having an affective mood disorder within the 12 months prior to the survey (ABS, 1998). Interestingly, both surveys revealed affective mood disorders were more prevalent in the female population (1.4 and 3.2% greater than males in 1997 and 2007, respectively). Depression is the fourth most common problem managed in general practice in Australia according to data on activity by General Practitioners (GP) for 2004–2005 (Black Dog Institute, 2010). In terms of all chronic conditions treated and managed by GPs, depression is second only to non-gestational hypertension (Britt et al., 2010). Furthermore, in addition to mortality associated with suicide, depressed patients are more likely to develop coronary heart disease (CHD) and type II diabetes. Depression also complicates the prognosis of a host of other chronic medical conditions (Evans et al., 2005).

Historically, much of the research into understanding the etiology and pathophysiology of depression has focused on genetics and environmental influences, while pharmacotherapeutic treatment regimes were based on the monoamine hypothesis of depression (Hirschfeld, 2000). Accordingly, SSRIs are still the most widely prescribed class of drug for depression (Young and Martin, 2003; Andrews et al., 2012). Nevertheless, there has been considerable effort to determine whether diet and nutritional factors play an important role in depression (Crowe, 2007; Martins, 2009; Akbaraly et al., 2013). Omega 3 fatty acids in particular represent an interesting area of research and are emerging as a potential agent in the treatment of depression (Logan, 2004; Martins, 2009).

Pathophysiology of depression

Despite its high prevalence and socioeconomic impact, the pathophysiology of depression is not well understood. Advances in neuroscience and neuroimaging techniques continue providing greater insight into the neurobiology of the brain

CONTACT Joseph Tucci j.tucci@latrobe.edu.au School of Pharmacy, La Trobe University, Edwards Rd. Victoria, Bendigo 3552, Australia.

(Krishnan, 2008), and afford means to study brain function and structure during episodes of affective mood disorders *in vivo*. Furthermore, results from neuroimaging studies may be combined with those from post mortem analyses (Drevets, 2000) for correlation, while therapeutic mechanisms involving specific treatments can be further analyzed (Siegle et al., 2012).

The role of monoamines

For over half a century the search for an understanding of the pathophysiology of depression centered on what was happening at the level of amine neurotransmitters and neuronal synapses. The monoamine hypothesis proposes that depression results from depletion of monoamine neurotransmitters, i.e., serotonin, noradrenaline, and dopamine, in the brain (Joyce, 2007). This hypothesis is now over 50 years old and arose from the empirical observation that depressive symptoms were influenced by the pharmacological manipulation of the monoaminergic system (Lanni, 2009; Sanacora, 2010). For instance, reserpine, an antihypertensive first introduced in 1954 (Lopez-Munoz et al., 2004), was found to deplete presynaptic stores of serotonin and/or noradrenaline and induce depression in some individuals. Iproniazid and imipramine, developed in the 1950s, had potent antidepressant effects in humans and were later shown to enhance central serotonin or noradrenaline transmission (Krishnan, 2008). Most antidepressant drugs are still designed to increase monoamine transmission either by inhibiting neuronal reuptake, e.g., tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), or by inhibiting monoamine degradation, e.g., monoamine oxidase inhibitors (MAOIs) (Parker, 2009).

Despite receiving considerable support, the monoamine hypothesis is considered inadequate by some researchers (Joyce, 2007), as it does not provide a comprehensive explanation for the actions of antidepressants, fails to explain why there should be only a gradual clinical response to antidepressant treatment when the increase in availability of monoamines is rapid, and why less than 50% of patients achieve full remission despite the numerous drugs available (Su, 2009).

Other neurotransmitters

Glutamate is the major mediator of excitatory synaptic transmission in the mammalian brain (Maletic, 2007). Abnormal function of the glutamergic system is implicated in the pathophysiology of several neurodegenerative disorders, such as Huntington's chorea, epilepsy, Alzheimer's disease, schizophrenia, and anxiety disorders (Siegel and Sanacora, 2012; Hashimoto et al., 2013). Increasing evidence suggests abnormal activity of the glutamatergic system observed in patients affected by mood disorders is likely to contribute to impairments in synaptic and neural plasticity found in patients with severe mood disorders (Lanni, 2009).

Gamma-aminobutyric acid (GABA) is the most widely distributed inhibitory neurotransmitter in the mammalian central nervous system (Celio, 1986; Thomson and Peterson, 2008). It is involved in the synaptic transmission of serotonin, dopamine, noradrenaline, and is thought to act as a modulator of neuronal function and numerous behavioral processes such as sleep, appetite, aggression, sexual behavior, pain, cardiovascular regulation, thermoregulation, and mood. Reduced GABA concentrations have been observed in the plasma and cerebrospinal fluid of depressed patients (Bhagwagar and Cohen, 2008). In addition, neuroimaging data has shown lowered levels of this molecule in specific areas of the brain such as the occipital cortex in depressed subjects (Price et al., 2009).

Proinflammatory cytokines

A growing body of research indicates that depression is associated with excessive production of pro-inflammatory cytokines (Logan, 2003; Dantzer et al., 2008). These cytokines, including interleukin-1beta (IL-1β), interleukin-2, interleukin-6, interferon-γ, and tumor necrosis factor-α (TNF-α) may lower neurotransmitter precursor availability and alter the metabolism of neurotransmitters and neurotransmitter transporter mRNAj (Logan, 2003). Furthermore, studies have shown that elevated IL-1β and TNF-α are associated with severity of depression (Suarez, 2003; Raison and Miller, 2013).

Stress response circuits

The analysis of available evidence suggests a direct correlation between stressful life events and increased vulnerability to affective disorders (Lanni, 2007). Corticotrophin releasing factor (CRF) initiates the hypothalamic pituitary adrenal (HPA) axis response to stress and has been a topic of interest in depression research (Shelton, 2007; Koob and Zorrilla, 2010). CRF is secreted from the hypothalamus which enhances secretion of adrenocorticotrophic hormone from the pituitary, in turn increasing glucocorticoid secretion from the adrenal cortex (Lee, 2010). Several human and animal model studies have reported hyperactivity of the HPA axis and elevated plasma cortisol concentrations in the majority of depressed subjects (Bale and Vale, 2004; Lee, 2010; Shekhar et al., 2011; Bailey et al., 2011).

Genetic Studies

In locating genes that predispose to depression, polymorphisms in the serotonin transporter (5-hydroxyl-tryptamine transporter (5-HTT)) gene have been extensively studied. Caspi et al., (2003) proposed that genetic changes to the 5-HTT linked polymorphism region (5-HTTLPR) may be linked to the propensity for stressful life events to give rise to depression. Nevertheless, while contributing genetic factors continue to be studied, the relationship between nucleotide polymorphisms of the 5-HTTLPR genotype and correlation with affective mood disorders have been shown to be more complex than previously thought (Clarke et al., 2010; Munaf$\int$ et al., 2009).

Neurotrophic factors and neuroplasticity

Developments in neuroscience have revealed that the adult brain does not have a fixed number of neurons that slowly die, but that adult brains are in a constant state of change—a concept referred to as "plasticity" (Joyce, 2007). In line with this concept, it is now thought that acute increases in the amount of synaptic monoamines induced by antidepressants produce

secondary neuroplastic changes that occur over a longer time frame and involve changes that mediate molecular and cellular plasticity (Krishnan and Nestler, 2008).

These developments have also fuelled interest in the role of neurotrophic growth factors in the development of depression. Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophic factor and promotes growth and development of immature neurons and enhances the survival and function of adult neurons (Krishnan and Nestler, 2008; Sen et al., 2008). It has been hypothesized that shrinkage of the hippocampus observed in depressed patients results from reduced levels of BDNF. Antidepressants increase the expression of neurotrophic factors in the hippocampus (Thomas and Peterson, 2008) suggesting treatment with antidepressants results in normalization of serum BDNF concentrations (Maleti, 2007).

Neural circuitry

Neuroimaging techniques have shown existence of highly interconnected neural circuits linking cortical, limbic and subcortical structures, including the prefrontal cortex, thalamus, amygdale, hippocampus, striatum, and hypothalamus (Maleti, 2007). Abnormalities of these neural circuits are likely associated with mood disorders (Joyce, 2007). Experiments employing functional magnetic resonance imaging and/or positron emission tomography have shown activity within the amygdale and subregions of the prefrontal cortex is correlated with dysphoric emotions (Krishnan and Nestler, 2008). Neuronal activity within these regions has been shown to increase transient sadness and chronic sadness in healthy and depressed individuals respectively, reverting to normal levels with successful treatment (Krishnan and Nestler, 2008).

Etiology of depression

Depression is a common psychiatric syndrome of complex etiology. A review of the relevant literature shows that the majority of earlier research concentrated on determining the genetic factors involved, environmental influence, or the relative importance of both (Thapar and McGuffin, 1996; Bebbington, 1998; Caspi et al., 2003).

Genetic studies

Early studies concluded that genetic factors may contribute to approximately 40% of cases of depression in both males and females, with the remainder attributable to the individual's environment (Thapar and McGuffin, 1996). Sulliavan et al., (2000) confirmed these findings in a meta-analysis of five methodologically rigorous twin studies that produced statistically homogeneous results and estimated that the heritability of major depression was 37%. Other studies also suggest that depression is familial, and that most or all of the familial aggregation results from genetic factors (Kendler et al., 2006).

Gender differences

While there is strong evidence that the risk of depression is greater in women than in men, it is unclear whether genetic factors are of relative equal importance in each gender and whether the same genetic factors predispose men and women to depression (Sullivan et al., 2000). Initially, researchers found that while women are consistently shown to have higher rates of major depression than men, major depression was found equally heritable in men and women, and most genetic risk factors influencing susceptibility to major depression are similar in both sexes (Kendler and Prescott, 1999). A meta-analysis of twin studies supported these findings by concluding that available evidence indicates similar genetic effects on predisposition to major depression in males and females (Sullivan, 2000). Interestingly, Kendler et al., (2001) studied male-female di-zygotic twins, same-sex mono-zygotic twins, and di-zygotic twins, and found that if broad definitions of illness are used, then the heritability of depression is greater in women. More recently, a study of a large Swedish twin series confirms these findings by showing the hereditability for depression is 29 and 42% in males and females, respectively (Kendler et al., 2006).

Environmental influences

While genetic factors appear to play an important role in the pathogenesis of depression, a range of environmental risk factors have also been implicated (Goldberg, 2006). Early experiences of parental care or neglect have a lasting influence on the likely onset of depression in adulthood, which is partially mediated by social factors including quality of core intimate relationships and stressful life events (Brown, 2008). Nevertheless, Kendler (2006) points out that identifying environmental risk factors for depression is not straightforward. Identified factors such as stressful life events, parenting, and social support networks are themselves influenced by genetic factors (Kendler, 2006), and although stressful life events are strong predictors for onset of depression, some argue that occurrence of a severe stressful life event has little effect in the absence of preexisting susceptibility (Brown, 2008). This research is supported in a review by Uher (2008) that states recent advances in neuroscience demonstrate genetic and environmental factors do not act in isolation. In fact, the effects of environmental factors depend on the genetic background of the individual and any impact of genetic variation on behavior is modified by the context of the environment. Such findings are leading researchers to consider multi-factor contextual perspectives rather than single-factor determinants in the etiology of depression (Uher, 2008).

Childhood experiences

Research into childhood maltreatment, e.g., sexual, physical, neglect, and emotional abuse, has demonstrated a clear link with higher rates of adult depression (Brown, 2008). Powers et al., (2009) further explored the relationship between childhood maltreatment, adult depression, and perceived social support. The results indicated that childhood emotional abuse and neglect proved more predictive of adult depression than sexual or physical abuse. Furthermore, perceived social support for females, in contrast to males, protected against adult depression even after accounting for contributions of both emotional abuse and neglect (Powers et al., 2009). In a study examining the extent to which childhood separation anxiety disorder (SAD)

confers risk for development of psychopathology during young adulthood (ages 19–30 years), Lewinsohn et al., (2008) found that SAD was a strong risk factor for the development of mental disorders with major vulnerabilities for panic disorder and depression.

Substance abuse

Several studies have shown that patients with major depressive disorder (MDD) have higher rates of nicotine and drug dependence (Connor et al., 2008; Levanthal et al., 2008). Excessive consumption of alcohol is likewise associated with a range of adverse outcomes, e.g., alcohol often plays a role in the three most common forms of youth mortality—motor vehicle accidents, homicides, and suicides (Mason et al., 2008). Evidence suggests also the high possibility of alcohol's role in the onset and progression of many psychiatric disorders including MDD (Mason et al., 2008).

Socioeconomic status

Research aimed at finding possible correlations between socioeconomic status and psychiatric disorders has shown that lower class individuals (by a variety of definitions) present higher rates of mental disorders (Eaton et al., 2001; Kosidou et al., 2011). Eaton et al., (2001) points out that the greatest risk factors for depression are (a) being female, (b) a family history of depression, and (c) stressful life events (i.e., death of family member) and that socioeconomic status as a causal factor is too simplistic. Causal factors were more specifically related to financial dependence, extreme poverty, high job demands, and the psychosocial work environment (Eaton et al., 2001).

Nutritional influences

Given that adequate intake of nutrients is essential for healthy mood, it is perhaps not surprising to find that the role of nutritional influences in depressive disorders has received much attention (Leung and Kaplan, 2009; Ruusunen et al., 2010; Shim et al., 2011). Nutrients are essential for optimal production of neurotransmitters affecting mood such as serotonin (derived from tryptophan, B group vitamins, and zinc as cofactors) (Kempler and Shannon, 2007). There is a growing body of published research supporting the hypothesis that intake of Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are of etiologic importance in depression (Colangelo et al., 2009; Lucas et al., 2009; Appleton et al., 2010).

Exercise

The use of exercise as an alternative to drug treatment for depression has received considerable attention. Exercise has been found to have both psychological effects (increased self-efficacy, reduced negative thought patterns) as well as biological effects such as alterations in adrenalin activity, reduced activity of the HPA axis, and increased secretion of endorphins that may explain its positive effect on mood (Brenes et al., 2007). Nevertheless, Mead et al., (2009) and Jesper et al., (2011) in two separate reviews reached similar conclusions: that any beneficial effects of exercise on depression was low and occurred over a short-term only.

Treatment of depression

Conventional treatment

Antidepressant medications are the first line of therapy in the treatment of depression. Since the development of the monoamine hypothesis in the 1960s, there has been intensive development of different agents that can be divided into four major classes of antidepressant drugs: TCAs, MAOIs, SSRIs, and SNRIs (Brunoni et al., 2009). These drugs are designed to increase monoamine transmission either by inhibiting neuronal reuptake (TCAs and SSRIs) or by inhibiting degradation (MAOIs) (Parker, 2009).

As an adjunct to medication, other therapies such as learning stress management techniques, psychotherapy, and cognitive behavioral therapy are valuable, and in the view of the authors, should be considered prior to, as well as during, pharmacotherapy. Electroconvulsive therapy, and repetitive transcranial magnetic stimulation offer alternative strategies, which may be useful when other strategies have yielded modest results (Brunoni et al., 2009).

Despite advances in pharmacotherapy and psychotherapies it is estimated that less than 50% of patients achieve full remission with optimized treatment (Su, 2009), and as many as 15–40% of depressed patients have treatment-resistant depression (Brunoni et al., 2009; Shelton et al., 2010). Consequently, much research is devoted to exploring new avenues of treatment. One of these is the role of n-3 PUFAs in the development and treatment of mood disorders.

Omega 3 polyunsaturated fatty acids

There are three types of naturally occurring fats classified by the number of carbon-carbon double bonds present in their fatty acid side chains: saturated, monounsaturated, and polyunsaturated. Further classification of those fatty acids containing one or more carbon-carbon double bonds (monounsaturated and polyunsaturated) is based on the isomeric configuration on the carbon-carbon double bond, *trans* or *cis* fatty acids. These differences in fatty acid structural configuration are known to affect changes in LDL and HDL serum cholesterol levels in humans (Mazaffarian et al., 2009). Polyunsaturated fats are further classified into two groups based on the position of the first carbon-carbon double bond site: n-3 and n-6 or the Omega 3 and Omega 6 PUFAs respectively. The most prominent n-6 PUFAs in the human diet are arachidonic acid (AA), found in meat, eggs, and diary products, and linoleic acid (LA) found in vegetable oils such as corn, safflower, sunflower, and soybean oils, and in commercially baked goods as well as fried foods and "fast" foods. LA can be indirectly converted to AA in the body and is the main PUFA in the western diet, comprising more than 85% of PUFA intake (Sontrop, 2006).

n-3 PUFAs are derived from alpha linolenic acid (ALA) which is found in canola, hemp, and walnuts as well as flaxseed which contains the highest concentrations (Logan, 2004). ALA is converted *in vivo* to eicosapentaenoic acid (EPA) and

docosahexaenoic acid (DHA) (Parker, 2006). This conversion of ALA to EPA and DHA is inefficient in humans with studies suggesting less than 1% of the ALA is metabolized (Sontrop, 2006). Seafood and in particular oily fish such as tuna, salmon, mackerel, and sardines are rich sources of pre-formed EPA and DHA. ALA and LA are termed essential fatty acids (EFAs) because they can not be synthesized by the body and must be derived from dietary sources (Sontrop, 2006).

Action of n-3 PUFAs

n-3 PUFAs appear to have two main biological functions. First, they are not only essential components of neuronal cell membranes, especially synaptic and dendritic membranes, but also intracellular membranes found in organelles such as mitochondria and vesicles. n-3 PUFAs, particularly DHA, play a vital role in maintaining cell membrane integrity and fluidity (Litman et al., 2001; Grossfield et al., 2006; Parker, 2006). Dietary fatty acids ultimately determine the composition of fatty acids within cell membranes. Increased concentrations of n-3 PUFAs produce a more fluid and biochemically efficient membrane. In contrast, low levels of n-3 PUFAs leads to increased incorporation of SFAs and cholesterol into the cell membrane phospholipids that cause the membrane to become more rigid (Das, 2006). Such changes in membrane fluidity affect the structure and/or functioning of proteins embedded in the membrane and influence the activity of membrane bound enzymes (Bowen and Clandinin, 2002), the number and affinity of receptors, the function of ion channels; the production and activity of neurotransmitters (Zimmer et al., 2000), signal transduction (Viadyanathan et al., 1994), neuronal growth factors, gene expression (Barcelo-Coblijn et al., 2003; Kitajka et al., 2004), as well as neuroplasticity and cell survival through the impact on neurotrophins such as BDNF (Yehuda, 2005; Owen et al., 2008; Conklin, 2010). n-3 PUFA deficiency also reduces the expression of brain glucose transporter GLUT1 (Pifferi et al., 2005).

Second, n-3 PUFAs and n-6 PUFAs give rise to bioactive molecules called eicosanoids including leukotrienes, prostaglandins, and thromboxanes. AA is the precursor of 2-series prostaglandins (PGE_2), thromboxanes (TXA_2), and the 4-series leukotrienes (LTB_4, LTC_4, and LTD_4). EPA is the precursor of the 3-series prostaglandins (PGE_3 and PGF_3), thromboxanes (TXA_3) and the 5-series leukotrienes (LTB_5, LTC_5, and LTD_5) (Das, 2006). Eicosanoids derived from AA are generally pro-inflammatory, proaggretory, and are involved in various pathological processes involving inflammation such as atherosclerosis, bronchial asthma, and inflammatory bowel disease (DeFilippis and Sperling, 2006). Eicosanoids derived from EPA are predominantly anti-inflammatory, inhibit platelet aggregation, and are therapeutic in clinical conditions such as collagen vascular diseases, hypertension, diabetes mellitus, metabolic syndrome X, psoriasis, eczema, atopic dermatitis, CHD, atherosclerosis, and cancer (Das, 2006). EPA and DHA reduce the production of pro-inflammatory eicosanoids by competing with AA for incorporation into cell membrane phospholipids and reducing cellular and plasma AA levels (Owen, 2008). DHA and EPA also inhibit the release of proinflammatory cytokines (Kiecolt-Glaser et al., 2007) such as interleukin-1β, interleukin-2, interleukin-6, interferon-γ, and TNFα, which depend on eicosanoid release (Parker, 2006).

EFA deficiency

Symptoms of EFA deficiency include fatigue, skin disorders, immune problems, weakness, gastrointestinal disorders, cardiovascular problems, growth retardation, and sterility. In addition, lack of dietary EFAs has been implicated in the development or aggravation of breast cancer, prostate cancer, rheumatoid arthritis, asthma, pre-eclampsia, depression, schizophrenia, and attention deficit and hyperactivity disorders, amongst others (Yehuda, 2005).

Possible mechanisms of n-3 PUFAs in depression

There are two main neurophysical mechanisms that have been proposed to explain the link between n-3 PUFAs and depression. A growing number of studies support the link between depression and production of pro-inflammatory cytokines (Parker, 2006). Some documented effects of these cytokines include lowered neurotransmitter precursor availability, activation of the HPA axis, and altered neurotransmitter metabolism (Logan, 2004). Furthermore, proinflammatory are not only surmised to be associated with the presence of depression, but to also act as indicators of the severity of the disease (Saurez *et al.*, 2003). Research has shown that patients with MDD are also likely to have elevated levels of inflammatory eicosanoids, particularly PGE_2 and thromboxane B_2. n-3 PUFAs are well documented inhibitors of both proinflammatory cytokines and inflammatory eicosanoids (Logan, 2003; Kiecolt-Glaser et al., 2007).

Another possible mechanism is the importance of n-3 PUFAs in maintaining membrane integrity and fluidity, which is crucial for neurotransmitter binding, and signaling within the cell (Su, 2009). Furthermore, n-3 PUFAs affect BDNF, which encourages synaptic plasticity, provides neuroprotection, enhances neurotransmission, and has antidepressant effects (Logan, 2003).

n-3 PUFAs and the Western diet

The dietary intake of n-3 PUFAs has dramatically declined in Western countries over the last century (Logan, 2004; Hayes et al., 2012). The ratio of n-6 to n-3 intake is estimated to be 20:1 in a modern Western diet, compared with that of our paleolithic ancestors who ate a diet richer in n-3 fatty acids and had an estimated ration of n-6:n-3 of 1.5:1 (Mazza et al., 2006). This dramatic dietary shift is thought related to overall reductions in fish consumption along with an increased consumption of domestically farmed fish. Not to mention, meat and fish contain less n-3 and more n-6 fatty acids than in the past due to use of commercial feeds high in n-6 and low in n-3 PUFA content (DeFilippis and Sperling, 2006).

Modern refining and processing of foods as well as cultural dietary selections, particularly in industrialized nations, have also led to an increase in the consumption on n-6 PUFAs and a relative deficiency of n-3 PUFAs (Young and Martin, 2003).

In contrast to this dramatic decline in the consumption of n-3 PUFAs is the rise in mood disorders (Parker, 2006; Sublette et al., 2006). A number of studies are now suggesting that this change in fatty acid intake is associated with the development of depression and the increase in suicidal tendency in those previously diagnosed with depression (Logan, 2004; Sublette

et al., 2006). Epidemiological studies support this link between n-3 PUFAs and depression.

n-3 PUFAs status and depression

Some workers have investigated levels of EFAs in human tissue and possible correlation of these with depression. Most studies have involved the analysis of fatty acid composition of phospholipids in plasma and red blood cells; and while it is acknowledged that phospholipid composition in the brain is not identical to serum, it is known that there are significant correlations between phospholipid composition in blood and brain (Horrobin, 2001).

In a review by Sontrop (2006) of published evidence linking n-3 PUFAs and depression, it was noted that with few exceptions, depressed subjects had lower concentrations of EPA and DHA and a higher ratio of n-6 to n-3 PUFAs compared to nondepressed subjects. Furthermore, these findings were supported subsequently by Kiecolt-Glaser et al., 2007. Studies conducted in other countries have consistently showed low concentrations ratios of n-6 to n-3 PUFAs in the plasma and red blood cells in depressed patients (Horrobin, 2001).

Feart et al., (2008) analyzed the relationship between plasma fatty acids and severity of depressive symptomatology in 1390 elderly citizens with a mean age of 74.6 years. Plasma EPA was lower in the subjects with depressive symptomatology than in the control subjects (0.85% compared with 1.01%; $P = 0.001$). Furthermore, higher plasma EPA was associated with a lower severity of depression, especially in those also taking antidepressants. Tiemeier et al., (2003) compared the plasma fatty acid composition of 264 subjects with depressive symptoms, including 106 with depressive disorders, against 461 randomly selected reference subjects. The subjects with depressive disorders had significantly lower concentrations of n-3 PUFAs (5.2% compared with 5.9%, $P = 0.02$) and a significantly higher ratio of n-6 to n-3 fatty acids (7.2 compared with 6.6, $P = 0.01$). As these results were not secondary to inflammation, atherosclerosis, or possible confounders, the authors concluded that plasma fatty acid composition appears to have a direct effect on mood. Mamalakis et al., (2002) investigated the possible relationship between fatty acids in adipose tissue and low mood in a group of 247 healthy adults. The mildly depressed subjects were found to have significantly lower adipose tissue DHA levels (34.6% less) than the nondepressed subjects.

In one of the few studies on brain tissue, researchers aimed to investigate whether brain fatty acids within the anterior cingulate cortex (BA-24) varied according to the presence of major depression at the time of death (Conklin, 2010). Using capillary gas chromatography, fatty acids were measured in a depressed group ($n = 12$) and in a control group without lifetime history of any diagnosed psychiatric conditions ($n = 14$). Compared to the control group, the depressed group showed significantly lower concentrations of numerous saturated and PUFAs including both the n-3 and n-6 fatty acids (Conklin, 2010).

Epidemiological studies

Empirical observations show that societies with a high consumption of fish, which is a rich source of n-3 PUFAs, appear to have a lower prevalence of depression (Su, 2009). In Japan, where annual fish consumption rates are estimated at 70 kg per person, prevalence rates of depression are 0.12%, compared to Germany, where annual fish consumption is less than 14 kg per person and the prevalence rate of depression is 5% (Young and Martin, 2003).

Hibbeln (1998) reported a very strong negative correlation between worldwide fish consumption and rates of major depression in a cross-national depression database analysis. Furthermore, a study by Magnasson et al., (2000) found an unexpectedly low incidence of seasonal affective disorder in Icelandic populations where fish consumption is high.

Interestingly, an ecological based analysis of published results from numerous countries (Hibbeln, 2002) found a positive correlation between seafood consumption, DHA concentration in human mother's milk, and a lower prevalence of postpartum depression.

Nevertheless, studies have also been conducted where no positive correlation between n-3 PUFA consumption, low mood, and depression or suicide have been reported. For example, a cohort study ($N = 29,133$) from a randomized double blind trial found no association between dietary intake of n-3 PUFAs and affective mood disorders (Hakkarainen, 2004).

Animal studies

Several laboratory investigations, using animal models, have been carried out to investigate the possible link between n-3 PUFAs and depression. Those fed a diet deficient in n-3 PUFAs show a reduction of in concentration of these throughout the brain cells and organelles along with a concomitant rise in n-6 PUFAs content. This alteration leads to a range of functional consequences in the monoamine transport system (Logan, 2003). A study by Chalon (2006) investigated this interaction between n-3 PUFA status and neurotransmission in rats chronically deficient in ALA (the precursor of n-3 PUFAs). Strong evidence that a profound n-3 PUFA deficiency alters particularly the dopaminergic and serotonergic transmission systems was found. Consequently, the author speculated that an imbalance in n-6:n-3 PUFAs could result in vulnerability in several neurological and psychiatric disorders (Chalon, 2006). Another animal model study by Ferraz et al., (2008) investigated the antidepressant effects of n-3 PUFAs in adult rats supplemented with fish oil during pregnancy and lactation, and rats supplemented post-weaning until adulthood. n-3 PUFA supplementation in both groups had a beneficial effect on preventing depression-like behavior compared to control groups.

Clinical studies

A case-control study within a cohort of middle-aged adult volunteers, investigated the association of fish and long-chain n-3 PUFA intakes with the occurrence of depressive episodes (Astorg et al., 2008). Dietary habits were assessed during the first 2 years of the follow-up and use of antidepressant medication (used as indications of depressive episodes) was recorded during the 8 year follow-up. Subjects consuming fatty fish or those with an intake of long-chain n-3 PUFA higher than 0.10% of energy intake had a significantly lesser risk of any

depressive episode and of recurrent depressive episodes, but not of single depressive episode. These associations were stronger in men and in nonsmokers and suggest that n-3PUFAs may contribute to the prevention of depression and especially recurrent depression (Astorg et al., 2008). These findings, however, are at odds with later reports from the same authors working on the same cohort. In the latter study, assessment of the fatty acid profiles of baseline serum phospholipids of volunteers showed no consistent association of depression risk with any serum fatty acid (Astorg et al., 2009). As part explanation for this discrepancy, the authors suggest that as fatty acids from erythrocyte membrane or adipose tissue better reflect longer term dietary intake, these biomarkers should instead be used in future studies, as they would possibly be more appropriate in assessing associations between long term PUFA status and depression (Astorg et al., 2009).

A clinical study investigating the use of n-3 PUFAs for the treatment of depression during pregnancy has been reported (Freeman et al., 2006). It is important to note that the study was very small, and so further research is required in order to add solidity to the data. Fifteen pregnant women with MDD participated in this flexible-dose, open-label trial. Subjects were assessed with the Edinburgh Postnatal Depression Scale (EPDS) and Hamilton Rating Scale for Depression. The average duration of participation was 8.3 weeks. The average final dose of EPA and DHA was 1.9 g/day resulting in a mean reduction in EPDS scores of 20.9% (SD = 21.9) and 34.1% (SD = 27.1) in HRDS scores (Freeman et al., 2006).

Treatment trials

Some of the trials discussed in this section were performed using limited numbers of participants, and so while the results may be suggestive, wider extrapolation is not necessarily possible. The earliest therapeutic trial of n-3 PUFAs in treating mood disorders, carried out in by Stoll et al., (1999), was one of the first to suggest positive effect of n-3 PUFAs in mood disorders, and inspired further research in this area. The preliminary double-blind, placebo-controlled trial, compared n-3 PUFAs (9.6 g/day) to placebo in addition to usual treatment over a four month period. Analysis of the cohort found that the n-3 PUFAs patient group had a significantly longer period of remission than the placebo group and for nearly every other outcome measure (based on various rating scales) the n-3 PUFA group performed better than placebo (Stoll et al., 1999). It is interesting to note that the trial was ended prematurely as it was deemed unethical to withhold treatment from the placebo group (Young and Martin, 2003).

Three years after this study interesting results emerged from a double blind placebo controlled trial (Nemets, 2002) investigating the addition of n-3 PUFAs (2 g EPA) to ongoing antidepressant medication for 20 subjects with recurrent unipolar depressive disorder, diagnosed according to DSM-IV. The patient's baseline scores on the HDRS were 18 or higher. Improvement in the treatment was significant from week 2, highly significant from week 3 and by the end of week 4 the mean reduction in the Hamilton Score was 12.4 points in the treatment group compared to 1.6 points for the placebo group (Nemets, 2002).

Peet and Horrobin (2002) studied the effects of varying doses of ethyl EPA in 70 patients with persistent depression despite ongoing treatment with adequate antidepressant medication. Each patient underwent assessment using the HDRS, the Montgomery-Asberg Depression Rating Scale, and the Beck Depression Inventory. The group taking 1 g EPA/day showed a significantly better outcome that the placebo group on all three rating scales. The 2 g EPA/day group showed little evidence of efficacy, and the 4 g EPA/day showed no significant changes toward improvement (Peet and Horrobin, 2002). No explanation was offered for the differing results with respect to increasing dose. It is interesting to note that while this study also confirmed the beneficial effects of n-3 PUFAs in depression, it appears that the importance of dose cannot be underestimated.

In a double-blind placebo-controlled trial over 8 weeks investigating addition of high dose fish oil (9.6 g/day) to standard antidepressant therapy in 28 patients with MDD, the treatment group showed significantly decreased scores on the HDRS ($P < 0.001$) compared to the placebo group (Su, 2003).

Despite these early results, not all of the earlier studies produced such positive outcomes. Marangell et al., (2003) carried out a randomized, double-blind, placebo-controlled trial of DHA monotherapy for patients with a major depressive episode. Thirty-six patients were randomly assigned to receive DHA dosage at 2 g/day or placebo for 6 weeks. The difference in response rates between the two groups did not reach statistical significance and the trial failed to show a significant effect of DHA monotherapy in people with MDD. The negative result in this study may reflect differing antidepressant effect of DHA and EPA.

More recently, a small, randomized, controlled, double-blind pilot study of n-3 PUFA treatment of childhood depression showed highly significant effects. Twenty children between the ages of 6 and 12 years who had been depressed for an average of 3 months participated in the study. They were randomly assigned to the treatment group or the placebo group.

Ratings were performed at baseline and at 2, 4, 8, 12, and 16 weeks using the Children's Depression Rating Scale (CDRS), Children's Depression Inventory, and Clinical Global Impression. The treatment group received 400 mg EPA + 200 mg DHA daily. In the treatment group, 7 of 10 children had a greater than 50% reduction in CDRS scores compared to 0 of 10 achieving greater than 50% reduction in CDRS scores in the placebo group. Four of 10 children in the n-3 PUFA group met the remission criteria of a CDRS score <29 at study exit, while no subject in the placebo group met this criteria (Nemets, 2006).

In a study by Frangou et al., (2006) examining the efficacy of EPA for treatment of depression and bi-polar disorder using a twelve week double-blind trial, individuals were randomly assigned to receive adjunctive treatment with EPA at 1 g/day, EPA 2 g/day, or placebo. Improvement was noted in the two treatment groups compared to the placebo group. Of particular interest is that there was no apparent benefit of EPA 2 g/day over the 1 g/day group, which confirms results from Peet and Horrobin's, 2002 study mentioned previously. In marked contrast to Frangou's et al., (2006) study, a randomized placebo-controlled trial of EPA in the treatment of bipolar depression

and rapid cycling bipolar disorder found absolutely no benefit of EPA 6 g/day (Keck et al., 2006). This study may well lend weight to the idea that the efficacy of EPA is dose dependent as discovered in the studies of Frangou et al., (2006) and Peet and Horrobin (2002).

Hallahan (2007) conducting a single centre, double-blind randomized control trial, assessed the efficacy of n-3 PUFAs in improving psychological well-being in patients with recurrent self-harm. At 12 weeks, the n-3 PUFA group had significantly greater improvements in scores for depression, suicidality, and daily stresses. Scores for impulsivity, aggression, and hostility did not differ.

Furthermore, work by Jazayeri et al., (2008) comparing the therapeutic effects of EPA, fluoxetine (a SSRI) and a combination of them in MDD, again showed positive results.

Sixty patients were randomly allocated to receive daily either EPA 1 g or 20 mg fluoxetine, or their combination for 8 weeks. Analysis found the EPA/fluoxetine combination to be significantly better than fluoxetine or EPA alone from the fourth week of treatment. Fluoxetine and EPA appeared to be equally effective in controlling depressive symptoms Jazayeri et al., (2008).

Further support for n-3 PUFAs as a prevention for psychotic disorders was also found in a randomized, double-blind, placebo controlled trial conducted between 2004 and 2007 (Amminger et al., 2010). A 12-week intervention period of 1.2 g/day n-3 PUFA or placebo was followed by a 40-week monitoring period. The total study of 12 months on 81 individuals at ultra-high risk of psychotic disorder concluded that n-3 PUFAs reduce the risk of progression to psychotic disorder with significant reduction in positive symptoms, negative symptoms, and general symptoms and improved functioning compared with placebo (Amminger et al., 2010).

Systematic review and meta-analyses

Appleton et al., (2006) completed a systematic review of published randomized, controlled trials investigating the effects of n-3 PUFAs on depressed mood. Twelve trials to 2006 were included in a meta-analysis. The authors concluded that the evidence examining the effects of n-3 PUFAs on depressed mood is limited and difficult to summarize and evaluate because results vary considerably.

Appleton et al., (2010) subsequently presented an updated systematic review and meta-analysis of the effects of n-3 long-chain PUFAs on depressed mood. Thirty five randomized controlled trials were identified, 17 of which were not included in the previous review. On this occasion, the authors concluded that while trial evidence of the effects of n-3 on depressed mood has increased, it remains difficult to summarize because of heterogeneity. The evidence suggests that there is some benefit of n-3 PUFAs in individuals with diagnosed depressive illness but no evidence of any benefit in individuals without a diagnosis of depressive illness (Appleton et al., 2010).

Another meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of n-3 fatty acids included 10 studies with treatment lasting 4 weeks or longer. In pooling the results of the 10 studies, the authors found a significant antidepressant effect of n-3 PUFAs. Patients with clearly defined depression or bipolar disorder significantly improved. Dose did not seem to change the antidepressant effect significantly (Lin and Su, 2007). Ross et al., (2007) critically reviewed the double blind placebo controlled clinical trials published prior to April 2007 to determine whether n-3 PUFAs are efficacious in a range of different psychiatric disorders. There was limited evidence in schizophrenia, borderline personality disorder, and attention deficit disorder. The most convincing evidence for the beneficial effects of n-3 PUFAs was found in mood disorders. A meta-analysis of trials involving patients with MDD and bipolar disorder provided evidence that n-3 PUFAs reduce symptoms of depression. It was suggested also that treatment with EPA may be more beneficial in mood disorders that DHA, although definite conclusions could not be made (Ross et al., 2007).

Safety

The overwhelming conclusion in the many studies reviewed is that PUFAs are generally well tolerated by both children and adults with mild gastrointestinal effects such as loose stools being the only consistently reported adverse event.

The US Department of Health and Human Services Agency for Healthcare Research and Quality identified 148 n-3 PUFA studies that reported on adverse events in 20,000 subjects. Dosage was up to 6 g/day fish oils. Gastrointestinal complaints were reported in 6.6% of the subjects taking n-3 PUFAs versus 4.3% in the placebo groups. Only one study reported an increased incidence of bleeding while 77 studies reported no adverse effects at all. The agency concluded that adverse effects of fish oils appear to be minor while the Food & Drug Administration has ruled that up to 3 g/day of EPA + DHA is safe (DeFilippis and Sperling, 2006).

In addition, these conclusions were further supported in a randomized, placebo controlled trial testing the safety of n-3 PUFAs in psychiatric patients. Seventy four patients with schizophrenia were treated with either 2 g/day EPA or placebo in addition to their antipsychotic medication. Forty patients continued the treatment of 2 g/day EPA in a 40-week open-label extension trial. Reporting of adverse events was similar for the two groups. Despite the EPA group showing a significant increase in bleeding time, it was concluded that 2 g/day EPA was well tolerated (Elmsley, 2007).

Conclusion

With the rising incidence of depression world-wide and the limited efficacy and unwanted side effects of current conventional antidepressants, there is increasing need for new treatments. In the past decade, there has been growing interest in the association between n-3 PUFAs and depression. n-3 PUFAs are essential components of neuronal cell membranes and play a vital role in a range of neurophysiological processes. Additionally, n-3 PUFAs are precursors to eicosanoids capable of reducing levels of proinflammatory eicosanoids and cytokines that are linked with depression.

Dietary intake of n-3 PUFAs has dramatically declined in western countries over the last century, coinciding with a rise in mood disorders. Epidemiological studies showing a

link between seafood consumption and mood disorders are compelling. Likewise, studies investigating n-3 PUFA status in depressed patients also show a positive correlation, with depressed patients having lower concentrations of n-3 PUFAs in plasma, red blood cells, adipose tissue, and brain tissue. A range of clinical studies and randomized, placebo-controlled trial have been carried out investigating the effects of n-3 PUFAs in depression as a stand-alone treatment or as an adjunct to prescribed medication. Studies varied considerably in the use of EPA, DHA, or a combination of both, and in the dose used. Notably, results from several studies appear to suggest that higher doses are not necessarily associated with greater benefits. Currently, there is no established clinically appropriate dose. Significantly, n-3 PUFAs have been shown to be generally well tolerated and associated with only minor adverse effects such as loose stools, in a range of populations.

Conclusions from systematic reviews and meta-analyses also vary considerably. Systematic reviews of published trials of the effect of n-3 PUFAS on depressed mood, concluded that the available evidence is difficult to evaluate and highlight the need for large, well-designed randomized controlled trials. Meta-analysis have reported that while clinical trials investigating the effects of n-3 PUFAs on depressed mood has increased, evaluation remains difficult due to the heterogeneity of the populations studied and the interventions used. Some meta-analyses have been more positive, showing that pooled evidence from trials shows support for the use of n-3 PUFAs in the treatment of mood disorders.

Therefore, while data from clinical trials remains equivocal, there appears adequate evidence to suggest that n-3 PUFAs can play a role in depression and deserve greater research. Such research may include: elucidation of whether the most clinically active component of fish oils is EPA, DHA, or a combination of both; whether n-3 PUFA supplementation alone has antidepressant effects or has greater potential augmenting standard antidepressants; to establish a clinically appropriate dose; and to further understand the role of n-3 PUFAs in the prevention and management of depression.

References

Akbaraly, T. N., Sabia, S., Shipley, M. J., Batty, G. D. and Kivimaki M (2013) Adherence to healthy dietary guidelines and future depressive symptoms: evidence for sex differentials in the Whitehall II study. *Am. J. Clin. Nutr.* **97**:419–427

Amminger, G. P., Schafer, M. R., Papageorgiou, K., Klier, C. M., Cotton, S. M., Harrigan, S. M., Mackinnon, A., Mcgorry, P. D. and Berger, G. E. (2010). Long-chain ω-3 fatty acids for indicated prevention of psychotic disorders. *Arch. Gen. Psychiatry.* **67**:146–154.

Andreescu, C., Mulsant, B. H. and Emanuel, J. E. (2008). Complementary and alternative medicine in the treatment of bipolar disorder - a review of the evidence. *J. Affect. Disord.* **110**:16–26.

Andrews P. W., Anderson Thomson Jr T., Amstadter A. and Neale M. C. (2012). Primum non nocere: an evolutionary analysis of whether antidepressants do more harm than good. *Psychology.* DOI: 10.3389/fpsyg.2012.00117

Appleton, K. M., Hayward, R. C., Gunnell, D., Peters, T. J., Rogers, P. J., Kessler, D. and Ness, A. R.(2006). Effects of n-3 long-chain polyunsaturated fatty acids on depressed mood: systematic review of published trials. *Am. J. Clin. Nutr.* **84**:1308–1316.

Appleton, K. M., Rogers, P. J. and Ness, A. R. (2010). Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. *Am. J. Clin. Nutr.* **91**:757–70.

Arteburn, L., Hall, E. B. and Oken, H. (2006). Distribution, interconversion, and dose response of n-3 fatty acids in humans1–4. *Am. J. Clin. Nutr.* 83(suppl):1467S–1476S.

Astorg, P., Couthouis, A., Bertrais, S., Arnault, N., Meneton, P., Guesnet, P., Alessandri, J. M., Galan, P. and Hercberg, S. (2008). Association of fish and long-chain n-3 polyunsaturated fatty acid intakes with the occurrence of depressive episodes in middle-aged French men and women. *Prostaglandins Leukot Essent Fatty Acids*. **78**:171–82.

Astorg, P., Bertrais, S., Alessandri, J. M., Guesnet, P., Kesse-Guyot, E., Linard, A., Lallemand, M. S., Galan, P. and Hercberg, S. (2009). Long-chain n-3 fatty acid levels in baseline serum phospholipids do not predict later occurrence of depressive episodes: a nested case-control study within a cohort of middle-aged French men and women. *Prostaglandins Leukot Essent Fatty Acids.* **81**:265–71.

Australian Bureau of Statistics (ABS) (2008). National Survey of Health and Wellbeing 2007 – Summary of Results.

Australian Federal Government: Australian Institute of Health and Welfare, viewed April 2010. http://www.aihw.gov.au/cdarf/datapages/incidenceprevalence

Barcelo-Coblijn, G., Hogyes, E., Kitajka, K., Puskas, L. G., Zvara, A., Hackler, L., Nyakas, C., Penke, Z. and Farkas, T. (2003). Modification by docosahexaenoic acid of age-induced alterations in gene expression and molecular composition of rat brain phospholipids. *Proc. Natl. Acad. Sci. USA.* **102**:10858–10863.

Bebbington, P. (1998). Sex and depression. *Psychol. Med.* **28**:1–8.

Bhagwagar, Z. and Cowen, P. (2008). "It's not over when it's over": persistent neurobiological abnormalities in recovered depressed patients. *Psychol. Med.* **38**:307–313.

Black Dog Institute, Victoria, Australia 2010. Viewed 19 April , 2010 http://www.blackdoginstitute.org.au/docs/FactsandFiguresfactsheet.pdf

Blumenthal, J. A., Babyak, M. A., Doraiswamy, P. M., Hoffman, B. M., Barbour, K. A., Herman, S., Craighead, W. E., Brosse, A. L., Waugh, R., Hinderliter, A. and Sherwood, A. (2007). Exercise and Pharmacotherapy in the treatment of Major Depressive Disorder. *Psychosom. Med.* **69**:587–596.

Bowen, B., Raffick, A. R., Clandinin, Michael, T (2002). Dietary low linolenic acid compared with docosahexaenoic acid alter synaptic plasma membrane phospholipid fatty acid composition and sodium-potassium ATPase kinetics in developing rats. *J. Neurochem.* **83**:764–774.

Brenes, G. A., Williamson, J. D., Messier, S. P., Rejeski, W. J., Pahor, M., IP, E. and Pennix, B. (2007). Treatment of Minor Depression in Older Adults: A Pilot Study Comparing sertraline and exercise. *Aging Ment. Health.* **11**:61–68

Brown, G. W., Craig, T. K. and Harris, T. O. (2008). Parental maltreatment and proximal risk factors using the Childhood Experience of Care and Abuse (CECA) instrument: a life-course study of adult chronic depression - 5. *J. Affect. Disord.* **110**:222–233

Brunoni, A. R., Fragnus, R. and Fregni, F. (2009). Pharmacological and Combined Interventions for the Acute Depressive Episode: Focus on Efficacy and Tolerability. *Ther. Clin. Risk Manag.* **5**:897–910.

Calder, P. (2006). n-3 Polyunsaturated fatty acids, inflammation, and inflammatory diseases 1–3 *Am. J. Clin. Nutr.* 83(suppl):1505S–1519S.

Caspi, A. (2003). Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene. *Science*. **301**:386.

Chalon, S. (2006). Omega 3 Fatty Acids and Monoamine Transmission. *Prostaglandins Leukot Essent Fatty Acids.* **75**:259–269.

Clarke, H., Flint, J., Attwood, A. S. and Munaf∫, M. R. (2010). Association of the 5- HTTLPR genotype and unipolar depression: a meta-analysis. *Psychol. Med.* **40**:1767–1778.

Colangelo, L. A., He, K., Whooley, M. A., Daviglus, M. L. and Liu, K. (2009). Higher dietary intake of long-chain omega-3 polyunsaturated fatty acids is inversely associated with depressive symptoms in women. *Nutrition.* **25**:1011–1019.

Conklin, S. M., Harris, J. I., Manuck, S. B., Yao, J. K., Hibbeln, J. R. and Muldoon, M. F. (2007). Serum omega-3 fatty acids are associated with variation in mood, personality and behavior in hypercholesterolemic community volunteers. *Psychiatry Res.* **152**:1–10.

Conklin, S. M., Manuck, S. B., Yao, J. K., Flory, J. D., Hibbeln, J. R. & Muldoon, M. F. (2007). High omega-6 and low omega-3 fatty acids are associated with depressive symptoms and neuroticism. *Psychosom Med.* **69**:932–934.

Conklin, S. M., Runyan, C., Leonard, S., Reddy, R. D., Muldoon, M. and Yao, J. K. (2010). Age-related changes of n-3 and n-6 Polyunsaturated Fatty Acids in the Anterior Cingulate Cortex of Individuals with Major Depressive Disorder. *Prostaglandins Leukot Essent Fatty Acids* **82**:111–119.

Connor, W. E. (2000). Importance of n-3 fatty acids in health and disease. *Am. J. Clin. Nutr.* **71**:171S–175S.

Crowe, F., Skeaff, M., Green, T. and Gray, A. (2007). Serum phospholipid n-3 long-chain polyunsaturated fatty acids and physical and mental health in a population-based survey of New Zealand adolescents and adults1–3 *Am. J. Clin. Nutr* **86**:1278–1285.

Das, U. N. 2006. Essential fatty acids: Biochemistry, physiology and pathology. *Biotechnical J.* **1**:420–439.

Defilippis, A. P. and Sperling, L. S. 2006. Understanding Omega-3′s. *Am. Heart J.* **151**:564–570.

Dunn, A. L. and Dishman, R. K. (1991). Exercise and the neurobiology of depression. *Exerc Sport Sci. Rev.* **19**:41–98.

Eaton, W. W., Muntaner, C., Borasso, G. and Smith, C. (2001). Socioeconomic Status and Depressive Syndrome: The Role of Inter-and Intra-Generational Mobility, Government Assistance and Work Environment. *J. Health Soc. Behav.* **42**:277–294.

Feart, C., Peuchant, E., Letenneur, L., Samieri, C., Montagnier, D., Fourrier-Reglat, A. and Barberger-Gateau, P. (2008). Plasma eicosapentaenoic acid is inversely associated with severity of depressive symptomatology in the elderly: data from the Bordeaux sample of the Three-City Study1–3. Am J Clin Nutr **87**:1156–1162.

Ferraz, A. C., Kiss, A., Araujo, R. L., Salles, H. M., Naliwaiko, K., Pamplona, J. and Matheussi, F. (2008). The antidepressant role of dietary long-chain polyunsaturated n-3 fatty acids in two phases in the developing brain. *Prostaglandins Leukot Essent Fatty Acids.* **78**:183–188.

Frangou, S., Lewis, M. and McCrone, P. (2006). Efficacy of ethyl-eicosapentaenoic acid in Bi-Polar Depression: a Randomised Double-Blind, Placebo-Controlled Trial. *Br. J. Psych.* **188**:46–50.

Freeman, M. P. (2009). Omega-3 fatty acids in major depressive disorder. *J Clin Psychiatry*, **70** Suppl 5:7–11.

Freeman, M. P., Hibbeln, J. R., Wisner, K. L., Davis, J. M., Mischoulon, D., Peet, M., Keck, P. E., Jr., Marangell, L. B., Richardson, A. J., Lake, J. and Stoll, A. L. (2006). Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J. Clin. Psychiatry.* **67**:1954–1967.

Gillespie, N., Whitfield, J., Williams, B., Heath, A. and Marin, N. (2005). The relationship between stressful life events, the serotonin transporter (5-HTTLPR) genotype and major depression. *Psychol. Med.* **35**:101–111.

Goldberg, D. (2006). The aetiology of depression. *Psychol. Med.* **36**:1341–1347.

Grossfield, A., Feller, S. E. and Pitman, M. C. (2006). A role for direct interactions in the modulation of rhodopsin by ω-3 polyunsaturated lipids. *Proc. Natl. Acad Sci. USA.* **103**:4888–4893.

Grenyer, B. F., Crowe, T., Meyer, B., Owen, A. J., Grigonis-Deane, E. M., Caputi, P. and Howe, P. R. (2007). Fish oil supplementation in the treatment of major depression: a randomised double-blind placebo-controlled trial. *Prog. Neuropsychopharmacol Biol. Psychiatry.* **31**:1393–1396.

Hakkarainen, R., Partonen, T., Haukka, J., Virtamo, J., Albanes, D. and Lonnqvist, J. (2004). Is low dietary intake of omega-3 fatty acids associated with depression? *Am. J. Psychiatry.* **161**:567–569.

Hallahan, B., Hibbeln, J. R., Davis, J. M. and Garland, M. R. (2007). Omega-3 fatty acid supplementation in patients with recurrent self-harm. Single-centre double-blind randomised controlled trial. *Br. J. Psychiatry.* **190**:118–122.

Hibbeln, J. (1998). Fish Consumption and major depression. *Lancet*. 351.

Hibbeln, J. and Davis, J. (2009). Considerations regarding neuropsychiatric nutritional requirements for intakes of omega-3 highly unsaturated fatty acids. *Prostaglandins, Leukotrienes and Essential Fatty Acids.* **81**:179–186.

Hibbeln, J. R. (2002). Seafood Consumption, the DHA Content of Mother's Milk and Prevalence Rates of Postpartum Depression: A Cross-national Ecological Analysis. *J. Affect. Disord.* **69**:15–29.

Hibbeln, J. R., Nieminen, L., Blasbal G, T., Riggs, J. and Lands, W. (2006). Healthy intakes of n-3 and n-6 fatty acids: estimations considering worldwide diversity1–5. *Am. J. Clin. Nut.* 83(suppl):1483S–1493S.

Horrobin, D. F. (2001). Phospholipid Metabolism and Depression: the possible roles of Phospholipase A_2 Co-enzyme A-Independent Transacylase. *Human Psychopharmacol Clin. Exp.* **16**:45–52.

Jazayeri, S., Tehrani-Doost, M., Keshavarz, S. A., Hosseini, M., Djazayery, A., Amini, H., Jalali, M. and Peet, M. (2008). Comparison of therapeutic effects of omega 3 fatty acid eicosapentaenoic acid and fluoxetin, separately and in combination, in major depressive disorder. *Aust. N Z J Psychiatry.* **42**:192–198.

Joyce, P. R. (2007). The evolving neurobiology of depression: from synapses to neurons, circuits and loops. *Aust N Z J Psychiatry.* **41**:561–562.

Kamphuis, M. H., Geerlings, M. I., Tijhuis, M. A., Kalmijn, S., Grobbee, D. E. and Kromhout, D. (2006). Depression and cardiovascular mortality: a role for n-3 fatty acids? *Am. J. Clin. Nutr.* **84**:1513–1517.

Keck, P. E., Jr., Mintz, J., Mcelroy, S. L., Freeman, M. P., Suppes, T., Frye, M. A., Altshuler, L. L., Kupka, R., Nolen, W. A., Leverich, G. S., Denicoff, K. D., Grunze, H., Duan, N. and Post, R. M. (2006). Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol. Psychiatry.* **60**:1020–1022.

Kemper, K. J. and Shannon, S. (2007). CAM Therapies to Promote Healthy Moods. *Pediat. Clin. North Am.* **54**:901.

Kendler, K. S. and Gardner, C. O. (2001). Monozygotic twins discordant for major depression: a preliminary exploration of the role of environmental experiences in the aetiology and course of illness. *Psychol. Med.* **31**:411–423.

Kendler, K. S., Gardner, C. O. and Lichtenstein, P. (2008). A developmental twin study of symptoms of anxiety and depression: evidence for genetic innovation and attenuation. *Psychol. Med.* **38**:1567–1575.

Kendler, K. S., Gatz, M., GardneR, C. O. and Pedersen, N. L. (2006). A Swedish national twin study of lifetime major depression. *Am. J. Psychiatry.* **163**:109–114.

Kendler, K. S., Myers, J. and Prescott, C. A. (2005). Sex differences in the relationship between social support and risk for major depression: a longitudinal study of opposite-sex twin pairs. *Am. J. Psychiatry.* **162**:250–256.

Kendler, K. S. and Prescott, C. A. (1999). A Population-Based Twin Study of Lifetime Major Depression in Men and Women. *Arch. Gen. Psychiatry.* **56**:39–44.

Kendler, K. S., Thornton, L. M. and Prescott, C. A. (2001). Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. *Am. J. Psychiatry.* **158**:587–593.

Kidd, P. M. (2007). Omega-3 DHA and EPA for cognition, behaviour, and mood: clinical findings and structural-functional synergies with cell membrane phospholipids. *Altern. Med. Rev.* **12**:207–227.

Kiecolt-Glaser, J. K., Belury, M. A., Porter, K. Beversdorf, D. Q., Lemeshow, S. and Glaser, R. (2007). Depressive symptoms, omega-**6**:omega-3 fatty acids, and inflammation in older adults. *Psychosomatic Med.* **69**:217–224.

Kitajka, K., Sinclair, A. J., Weisinger, R. S., Weisinger, H. S., Mathai, M., Jayasooriya, A. P., Halver, J. E. and Puskas, L. G. (2004). Effects of dietary omega-3 polyunsaturated fatty acids on brain gene expression. *Porc. Natl. Acad Sci. USA.* **101**:10931–10936.

Kosidou, K., Dalman, C., Lundberg, M., Hallqvist, J., Isacsson, G. and Magnusson, C. (2011). Socioeconomic status and risk of psychological distress and depression in the Stockholm Public Health Cohort: A population-based study. *J. Affect. Disord.* **134**:160–167.

Krishnan, V. and Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature.* **455**:894–902.

Krogh J., Nordentoft M., Sterne J. and Lawlor D. (2010). The Effect of Exercise in Clinically Depressed Adults: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *CNS Drugs.* **24**:131–161.

Lanfumey, L. and Hamon, M. (2005). Neurobiology of depression: new data. *Therapie.* **60**:431–440.

Lanni, C., Govoni, S., Lucchelli, A. and Boselli, C. (2009). Depression and antidepressants: molecular and cellular aspects. *Cell Mol. Life Sci.* **66**:2985–3008.

Leung, B. M. and Kaplan, B. J. (2009). Perinatal depression: prevalence, risks, and the nutrition link–a review of the literature. *J. Am. Dietetic Assoc.* **109**(9):1556.

Leventhal, A. M., Witt, C. F. and Zimmerman, M. (2008). Associations between Depression Subtypes and Substance Use Disorders. *Psychiatry Res.* **161**:43–50.

Lewinsohn, P. M., Holm-Denoma, J. M., Small, J. W., Seeley, J. R. and Joiner, T. E. (2008). Separation Anxiety Disorder in Childhood as a Risk Factor for Future Mental Illness. *J. Am. Acad. Child Adolesc. Psychia.* **47**:548–555.

Lin, P. Y. and Su, K. P. 2007. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *J. Clin. Psychiatry.* **68**:1056–1061.

Litman, B. J., Niu, S-L. Polozova, A. and Mitchell, D. C. (2001). The role of docosahexaenoic acid containing phospholipids in modulating G protein-coupled signalling pathways. *J. Mol. Neurosci.* **16**:237–242.

Logan, A. C. (2003). Neurobehavioral aspects of omega-3 fatty acids: possible mechanisms and therapeutic value in major depression. *Altern. Med. Rev.* **8**:410–425.

Logan, A. C. (2004). Omega-3 fatty acids and major depression: A primer for the mental health professional. *Lipids Health Dis.* **3**:25.

Logan, A. C. (2005). Omega-3 and depression research: hold the olive oil. *Prostaglandins Leukot Essent Fatty Acids.* **72**:441.

López-Muñoz, F., Bhatara, V. S., Alamo, C. and Cuenca, E. (2004) Historical approach to reserpine discovery and its introduction in psychiatry. *Actas Esp Psiquiatr.* **32**:387–395.

Lucas, M., Asselin, G., Merette, C., Poulin, M. J. and Dodin, S. (2009). Ethyl-eicosapentaenoic acid for the treatment of psychological distress and depressive symptoms in middle-aged women: a double-blind, placebo-controlled, randomized clinical trial. *Am. J. Clin. Nutr.* **89**:641–651.

Magnusson, A., Axelsson, J., Karlsson, M. and Oskarsson, H. (2000). Lack of Seasonal Mood Change in the Icelandic Population: Results of a Cross-Sectional Study. *Am. J. Psychiatry.* **157**:234–238.

Maletic, V., Robinson, M., Oakes, T., Iyengar, S., Ball, S. G. and Russell, J. (2007). Neurobiology of depression: an integrated view of key findings. *Int. J. Clin. Pract.* **61**:2030–2040.

Mamalakis, G., Tornaritis, M. and Kafatos, A. (2002). Depression and adipose essential polyunsaturated fatty acids. *Prostaglandins, Leuk and Ess Fat Ac.* **67**:311–318.

Marangell, L. B., Martinez, J. M., Zboyan, H. A., Kertz, B., Kim, H. F. and Puryear, L. J. (2003). A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am. J. Psychiatry.* **160**:996–998.

Martins, J. G. (2009). EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. *J. Am. Coll. Nutr.* **28**:525–542.

Mason, W. A., Kosterman, R., Haggerty, K. P., Hawkins, J. D., Redmond, C., Spoth, R. L. and Shin, C. (2008). Dimensions of Adolescent Alcohol Involvement as Predictors of Young-Adult Major Depression. *J. Stud. Alcohol Drugs.* **69**:275–285.

Mazza, M., Pomponi, M., Janiri, L., Bria, P. and Mazza, S. (2006). Omega 3 fatty acids and antioxidants in neurological and psychiatric disease: an overview. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* **31**:12–26.

Mcnamara, R. K. (2006). The emerging role of omega-3 fatty acids in psychiatry. *Prostaglandins, Leukot Essent Fatty Acids.* **75**:223–225.

Mcnamara, R. K., Ostrander, M., Abplanalp, W., Richtand, N. M., Benoit, S. C. and Clegg, D. J. (2006). Modulation of phosphoinositide-protein kinase C signal transduction by omega-3 fatty acids: implications for the pathophysiology and treatment of recurrent neuropsychiatric illness. *Prostaglandins Leukot Essent Fatty Acids.* **75**:237–257.

Mead, G. E., Morley, W., Campbell, P., Greig, C. A., McMurdo, M. and Lawlor, D. A. (2009). Exercise for depression. *Cochrane Database Syst Rev.* **3**.

Mitchell, P., Slade, T. and Andrews, G. (2004). Twelve-month prevalence and disability of DSM-IV bipolar disorder in an Australian general population survey. *Psychol. Med.* **34**:777–785.

Munaf∫, M. R., Freimer, N. B., Ng, W., Ophoff, R., Veijola, J., Miettunen, J., Järvelin, M. R., Taanila, A. and Flint, J. (2009). 5-HTTLPR genotype and anxiety-related personality traits: a meta-analysis and new data. *Am. J. Med. Genet. B Neuropsychiatr Genet.* 150B:271–281

Nemets, B., Stahl, Z. and Belmaker, R. H. (2002). Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am. J. Psychiatry.* **159**:477–479.

Nemets, H., Nemets, B., Apter, A., Bracha, Z. and Belmaker, R. H. (2006). Omega 3 Treatment of Childhood Depression: A Controlled Double-Blind Pilot Study. *Am. J. Psychiatry.* **163**:1098–1100.

Nestler, E. J., Barrot, M., DileonE, R. J., Eisch, A. J., Gold, S. J. and Monteggia, L. M. (2002). Neurobiology of depression. *Neuron.* **34**:13–25.

Oquendo, M. A. and Parsey, R. V. 2007. What have we learned about the neurobiology of major depression? *Am. J. Psychiatry.* **164**:540–2.

Owen, C., Rees, A. M. and Parker, G. (2008). The role of fatty acids in the development and treatment of mood disorders. *Curr. Opin. Psychiatry.* **21**:19–24.

Parker, G. (2009). Antidepressants on trial: how valid is the evidence? *Br. J. Psychiatry.* **194**:1–3.

Parker, G., Gibson, N. A., Brotchie, H., Heruc, G., Rees, A. M. and Hadzi-Pavlovic, D. (2006). Omega-3 fatty acids and mood disorders. *Am. J. Psychiatry.* **163**:969–78.

Peet, M. (2003). Eicosapentaenoic acid in the treatment of schizophrenia and depression: rationale and preliminary double-blind clinical trial results. *Prostaglandins Leukot Essent Fatty Acids.* **69**:477–85.

Peet, M. and Horrobin, D. (2002). A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch. Gen. Psychiatry.* **59**:913–919.

Pifferi, F., Roux, F., Langelier, B., Alessandri, J-M., Vancassel, S., Jouin, M., Lavaille, M. and Guesnet, P. (2005). (n-3) polyunsaturated fatty acid deficiency reduces the expression of both isoforms of the brain glucose transporter GLUT1 in rats. *J. Nutrition.* **135**:2241–2246.

Powers, A., Rossler, K. and Bradley, R. (2009). The Protective Role of Friendship on the Effects of Childhood Abuse and Depression. *Depress. Anxiety.* **26**:46–52.

Raison C. L. and Miller A. H. (2013). Role of Inflammation in Depression: Implications for Phenomenology, Pathophysiology and Treatment. In: Halaris, A., Leonard, B. E. (eds): Inflammation in Psychiatry. Mod Trends Pharmacopsychiatry. Basel, Karger, 2013, vol 28, pp. 33–48.

Ross, B. M. (2009). Omega-3 polyunsaturated fatty acids and anxiety disorders. *Prostaglandins Leukot Essent Fatty Acids.* **81**:309–12.

Ross, B. M., Seguin, J. and Sieswerda, L. E. (2007). Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid? *Lipids Health Dis.* **6**:21.

Ruusunen, A., Lehto, S. M., Tolmunen, T., Mursu, J., Kaplan, G. A. and Voutilainen, S. (2010). Coffee, tea and caffeine intake and the risk of severe depression in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Public health Nutr.* **13**:1215–1220.

Sanacora, G. (2010). Cortical inhibition, gamma-aminobutyric acid, and major depression: there is plenty of smoke but is there fire? *Biol. Psychiatry.* **67**:397–398.

Shelton, R. C. (2007). The molecular neurobiology of depression. *Psychiatr Clin. North Am.* **30**:1–11.

Shelton R. C., Olawale Osuntokun A., Heinloth N. and Corya S. A. (2009) Therapeutic Options for Treatment-Resistant Depression. *Eur. J. Clin. Nutr.* (2009). **63**:S5–S21.

Shim, R. S., Baltrus, P., Ye, J. and Rust, G. (2011). Prevalence, treatment, and control of depressive symptoms in the United States: results from the National Health and Nutrition Examination Survey (NHANES), 2005–2008. *J. Am. Board Fam. Med.* **24**(1):33–38.

Siegel, S. and Sanacora, G. (2012). The roles of glutamate receptors across major neurological and psychiatric disorders. *Pharmacol. Biochem. Behav.* **100**:653–655.

Silvers, K. M., Woolley, C. C., Hamilton, F. C., Watts, P. M. and Watson, R. A. (2005). Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukot Essent Fatty Acids.* **72**:211–8.

Sontrop, J. and Campbell, M. K. (2006). Omega-3 polyunsaturated fatty acids and depression: a review of the evidence and a methodological critique. *Prev. Med.* **42**:4–13.

StahL, L. A., Begg, D. P., Weisinger, R. S. and Sinclair, A. J. (2008). The role of omega-3 fatty acids in mood disorders. *Curr. Opin. Investig. Drugs.* **9**:57–64.

Stoll, A. L., Severus, W. E., Freeman, M. P., Rueter, S., Zboyan, H. F., Diamond, E., Cress, K. K. and Marangell, L. B. 1999. Omega 3 Fatty Acids and Bi-Polar Disorder. A Preliminary Double-Blind, Placebo-Controlled Trial. *Arch. Gen. Psychiatry.* **56**:407–412.

Strom, M., Mortensen, E. L., Halldorsson, T. I., Thorsdottir, I. and Olsen, S. F. (2009). Fish and long-chain n-3 polyunsaturated fatty acid intakes during pregnancy and risk of postpartum depression: a prospective study based on a large national birth cohort. *Am. J. Clin. Nutr.* **90**:149–55.

Su, K. P. (2008). Mind-body interface: the role of n-3 fatty acids in psychoneuroimmunology, somatic presentation, and medical illness comorbidity of depression. *Asia Pac.J. Clin. Nutr.* **17** Suppl 1:151–157.

Su, K. P. (2009). Biological mechanism of antidepressant effect of omega-3 fatty acids: how does fish oil act as a 'mind-body interface'? *Neurosignals.* **17**:144–152.

Su, K.-P., Huang, S.-Y., Chiu, C.-C. and Shen, W. W. (2003). Omega 3 Fatty Acids in Major Depressive Disorder. A Preliminary Double-Blind, Placebo-Controlled Trial. *Eur. Neuropsychopharmacology.* **13**:267–271.

SuareZ, E., Krishnan, R. and Lewis, J. (2003). The Relation of Severity of Depressive Symptoms to Monocyte-Associated Proinflammatory Cytokines and Chemokines in Apparently Healthy Men. *Psychosom. Med.* **65**:362–368.

Sublette, M. E., Hibbeln, J. R., Galfalvey, H., Oquendo, M. A. and Mann, J. J. (2006). Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. *Am. J. Psychiatry.* **163**:1100–1102.

Sullivan, P., Neale, M. and Kendler, K. S. (2000). Genetic Epidemiology of Major Depression: Review and Meta-Analysis. *Am. J. Psychiatry.* 1552–1562.

Taylor, A. and Kim-Cohen, J. (2007). Meta-analysis of gene–environment: interactions in developmental psychopathology. *Dev. Psychopathol.* **19**:1029–1037.

Thapari, A. and Mcguffin, P. (1996). Genetic influences on life events in childhood. *Psychol. Med.* **26**:813–820.

The Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. Washington DC: American Psychiatric Association Press; 1994.

Thomas, R. and Peterson, D. (2008). Even Neural Stem Cells Get the Blues: Evidence for a Molecular Link Between Modulation of Adult Neurogenesis and Depression. *Gene Expression.* **14**:183–193.

Tiemeier, H., Van Tuijl, H. R., HofmaN, A., Kiliaan, A. J. and Breteler, M. (2003). Plasma fatty acid composition and depression are associated in the elderly: the Rotterdam Study. *Am. J. Clin. Nutr.* **78**:40–6.

Timonen, M., Horrobin, D., Jokelainen, J., Laitinen, J., Herva, A. and Rasanen, P. (2004). Fish consumption and depression: the Northern Finland 1966 birth cohort study. *J. Affect. Disord.* **82**:447–52.

Uher, R. (2008). The implications of gene-environment interactions in depression: will cause inform cure? *Mol. Psychiatry.* **13**:1070–8.

Vaidyanathan, V. V., Raja Rao, K. V. and Sastry, P. S. (1994). Regulation of diacylglycerol kinase in rat brain membranes by docosahexaenoic acid. *Neurosci. Lett.* **179**:171–174.

World Health Organisation (WHO), Mental health, Depression, viewed April 2010 http://www.who.int/mental_health/management/depression/definition/en/

World Health Organisation (WHO) (2012). Fact Sheet No. 369 October 2012

Yehuda, S., Rabinovitz, S. and Mostofsky, D. (2005). Essential fatty acids and the brain: from infancy to aging. *Neurobiol. Aging.* **26**:S98–S102.

Young, C. and Martin, A. 2003. Omega-3 fatty acids in mood disorders: an overview. *Rev. Bras Psiquiatr.* **25**:184–187.

Zimmer, L., Delion-Vancassel, S., Durand, G., Guilloteau, D., Bodard, S., Besnard, J.-C. and Chalon, S. (2000). Modification of dopamine transmission in the nucleus accumbens of rats deficient in n-3 polyunsaturated fatty acids. *J. Lipid Res.* **41**:32–40.