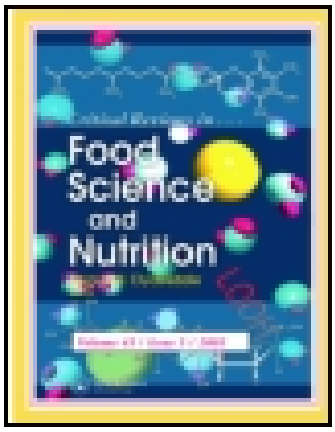

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Omega 3 Polyunsaturated Fatty Acids and the Treatment of Depression

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Omega 3 Polyunsaturated Fatty Acids and the Treatment of Depression.

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Abstract:

Depression is a common, recurrent, and debilitating illness that has become more prevalent over the past 100 years. This report reviews the aetiology 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 (SSRI) 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 randomised 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 Organisation 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 behavioural problems termed 'affective' or mood disorders. The world Mental Health Survey, which was a study across 17 countries, reported that five percent 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 18y and 65y) 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 16y 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 aetiology 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 (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 analysed (Siegle *et al*., 2012).

The role of monoamines:

For over half a century the search for an understanding of the pathophysiology of depression centred 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 mono-aminergic system (Lanni 2009; Sanacora 2010). For instance, reserpine, an antihypertensive first introduced in 1954 (Lopez-Munoz *et al*., 2004), was found to deplete pre-synaptic 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 behavioural processes such as sleep, appetite, aggression, sexual behaviour, 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).

Pro-inflammatory 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 tumour 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 (ACTH) 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; Munafò *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 hypothesised 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 normalisation 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 (fMRI) and/or positron emission tomography (PET) have shown activity within the amygdale and sub-regions of the pre-frontal 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).

Aetiology of depression:

Depression is a common psychiatric syndrome of complex aetiology. 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 pre-existing 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 behaviour 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 aetiology 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 19y to 30y), 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 co-factors) (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 aetiologic 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 mono-amine hypothesis in the 1960s there has been intensive development of different agents that can be divided into four major classes of antidepressant drugs: tricyclic antidepressants (TCAs); monoamine oxidase inhibitors (MAOIs); selective serotonin reuptake inhibitors (SSRIs); and serotonin-noradrenaline ruuptake inhibitors (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 behavioural therapy (CBT) are valuable, and in the view of the authors, should be considered prior to, as well as during, pharmacotherapy. Electroconvulsive therapy (ECT), and repetitive transcranial magnetic stimulation (rTMS) 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 (TRD) (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 (n-3 PUFAs). 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 polyunsaturated fatty acid (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 ande 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. Firstly, they are 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).

Secondly, 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, LTD_4). EPA is the precursor of the 3-series prostaglandins (PGE_3, PGF_3), thromboxanes (TXA_3) and the 5-series leukotrienes (LTB_5, LTC_5, LTD_5) (Das 2006). Eicosanoids derived from AA are generally pro-inflammatory, pro-aggretory, 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, coronary heart disease (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 pro-inflammatory 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, pro-inflammatory 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 pro-inflammatory 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 signalling 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 industrialised 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 non-depressed 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) analysed 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 non-depressed 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 polyunsaturated fatty acids 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 70kg per person, prevalence rates of depression are 0.12%, compared to Germany, where annual fish consumption is less than 14kg per person and the prevalence rate of depression is 5% (Young and Martin 2003).

Hibbeln (1998) reported a very strong negative correlation between world- wide 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 anti-depressant 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 non-smokers 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 (HRSD). The average duration of participation was 8.3 weeks. The average final dose of EPA and DHA was 1.9g/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 (9.6g/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 (2g 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 1g EPA/day showed a significantly better outcome that the placebo group on all 3 rating scales. The 2g EPA/day group showed little evidence of efficacy, and the 4g 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 (9.6g/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 2g/day or placebo for 6 weeks. The difference in response rates between the 2 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. 20 children between the ages of 6- 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 (CDI), and Clinical Global Impression (CGI). The treatment group received 400mg EPA + 200mg DHA daily. In the treatment group, 7 out of 10 children had a greater than 50% reduction in CDRS scores compared to 0 out of 10 achieving greater than 50% reduction in CDRS scores in the placebo group. Four out 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 1g/day, EPA 2g/day, or placebo. Improvement was noted in the 2 treatment groups compared to the placebo group. Of particular interest is that there was no apparent benefit of EPA 2g/day over the 1g/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 6g/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 1g 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 6g/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 (FDA) has ruled that up to 3g/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 2g/day EPA or placebo in addition to their anti-psychotic medication. Forty patients continued the treatment of 2g/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 2g/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 pro-inflammatory 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 randomised, 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 randomised 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 anti-depressant 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.

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