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. 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 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 *et al*., 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 *et al*., 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

70 therapeutic mechanisms involving specific treatments can be further analysed (Siegle *et*
71 *al*., 2012).

72 **The role of monoamines:**

73 For several years the search for an understanding of the pathophysiology of depression
74 centred on what was happening at the level of amine neurotransmitters and neuronal
75 synapses. The monoamine hypothesis proposes that depression results from depletion of
76 monoamine neurotransmitters, i.e., serotonin, noradrenaline, and dopamine, in the brain
77 (Joyce 2007). This hypothesis is now over 40 years old and arose from the empirical
78 observation that depressive symptoms were influenced by the pharmacological
79 manipulation of the mono-aminergic system (Lanni 2009; Sanacora 2010). For instance,
80 reserpine, an antihypertensive first introduced in 1954 (Lopez-Munoz *et al*., 2004), was
81 found to deplete pre-synaptic stores of serotonin and/or noradrenaline and induce
82 depression in some individuals. Iproniazid and imipramine, developed in the 1950s, had
83 potent antidepressant effects in humans and were later shown to enhance central
84 serotonin or noradrenaline transmission (Krishnan 2008). Most antidepressant drugs are
85 still designed to increase monoamine transmission either by inhibiting neuronal reuptake,
86 e.g., tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs),
87 serotonin noradrenaline reuptake inhibitors (SNRIs), or by inhibiting monoamine
88 degradation, e.g., monoamine oxidase inhibitors (MAOIs) (Parker 2009).
89 Despite receiving considerable support, the monoamine hypothesis is considered
90 inadequate by some researchers (Joyce 2007), as it does not provide a comprehensive
91 explanation for the actions of antidepressants, fails to explain why there should be only a
92 gradual clinical response to antidepressant treatment when the increase in availability of

93 monoamines is rapid, and why less than 50% of patients achieve full remission despite
94 the numerous drugs available (Su 2009).
95 **Other neurotransmitters:**
96 **Glutamate** is the major mediator of excitatory synaptic transmission in the mammalian
97 brain (Maletic 2007). Abnormal function of the glutamergic system is implicated in the
98 pathophysiology of several neurodegenerative disorders, such as Huntington's chorea,
99 epilepsy, Alzheimer's disease, schizophrenia, and anxiety disorders (Siegel and Sanacora
100 2012; Hashimoto *et al*., 2013). Increasing evidence suggests abnormal activity of the
101 glutamatergic system observed in patients affected by mood disorders is likely to
102 contribute to impairments in synaptic and neural plasticity found in patients with severe
103 mood disorders (Lanni 2009).
104 **Gamma-aminobutyric acid** (GABA) is the most widely distributed inhibitory
105 neurotransmitter in the mammalian central nervous system (Celio 1986; Thomson and
106 Peterson 2008). It is involved in the synaptic transmission of serotonin, dopamine,
107 noradrenaline, and is thought to act as a modulator of neuronal function and numerous
108 behavioural processes such as sleep, appetite, aggression, sexual behaviour, pain,
109 cardiovascular regulation, thermoregulation, and mood. Reduced GABA concentrations
110 have been observed in the plasma and cerebrospinal fluid of depressed patients
111 (Bhagwagar and Cohen 2008). In addition, neuroimaging data has shown lowered levels
112 of this molecule in specific areas of the brain such as the occipital cortex in depressed
113 subjects (Price *et al*., 2009).
114 **Pro-inflammatory cytokines.** A growing body of research indicates that depression is
115 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 mood 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 the 5-HTT linked polymorphism region (5-HTTLPR) underwent modification which could explain the discordance seen between stressful life events and the occurrence of depression in populations. 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; Munafo 2012).

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 account for approximately 40% of the cause 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, 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

208 factors do not act in isolation. In fact, the effects of environmental factors depend on the
209 genetic background of the individual and any impact of genetic variation on behaviour is
210 modified by the context of the environment. Such findings are leading researchers to
211 consider multi-factor contextual perspectives rather than single-factor determinants in the
212 aetiology of depression (Uher 2008).
213 **Childhood Experiences**. Research into childhood maltreatment, e.g., sexual, physical,
214 neglect, and emotional abuse, has demonstrated a clear link with higher rates of adult
215 depression (Brown 2008). Powers *et al*., (2009) further explored the relationship between
216 childhood maltreatment, adult depression, and perceived social support. The results
217 indicated that childhood emotional abuse and neglect proved more predictive of adult
218 depression than sexual or physical abuse. Furthermore, perceived social support for
219 females, in contrast to males, protected against adult depression even after accounting for
220 contributions of both emotional abuse and neglect (Powers *et al*., 2009). In a study
221 examining the extent to which childhood separation anxiety disorder (SAD) confers risk
222 for development of psychopathology during young adulthood (ages 19y to 30y),
223 Lewinsohn *et al*., (2008) found that SAD was a strong (78.6%) risk factor for the
224 development of mental disorders with major vulnerabilities for panic disorder and
225 depression.
226 **Substance Abuse**. Several studies have shown that patients with major depressive
227 disorder (MDD), including subtypes of MDD, have higher rates of nicotine and drug
228 dependence (Connor *et al*., 2008; Levanthal *et al*., 2008). Excessive consumption of
229 alcohol is likewise associated with a range of adverse outcomes, e.g., alcohol often plays
230 a role in the three most common forms of youth mentality – 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, cognitive behavioural therapy (CBT), electroconvulsive therapy (ECT), and repetitive transcranial magnetic stimulation (rTMS) offer alternative strategies (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

368 that of our paleolithic ancestors who ate a diet richer in n-3 fatty acids and had an
369 estimated ration of n-6:n-3 of 1.5:1 (Mazza *et al*., 2006). This dramatic dietary shift is
370 thought related to overall reductions in fish consumption along with an increased
371 consumption of domestically farmed fish. Not to mention, meat and fish contain less n-3
372 and more n-6 fatty acids than in the past due to use of commercial feeds high in n-6 and
373 low in n-3 PUFA content (DeFilippis and Sperling 2006).
374 Modern refining and processing of foods as well as cultural dietary selections,
375 particularly in industrialised nations, have also led to an increase in the consumption on
376 n-6 PUFAs and a relative deficiency of n-3 PUFAs (Young and Martin 2003).
377 In contrast to this dramatic decline in the consumption of n-3 PUFAs is the rise in mood
378 disorders (Parker 2006; Sublette *et al*., 2006). During the past 100 years the incidence of
379 major depression in western societies has increased while the age of onset has decreased.
380 A number of studies are now suggesting that this change in fatty acid intake is associated
381 with the development of depression (Logan 2004; Sublette *et al*., 2006). Epidemiological
382 studies support this link between n-3 PUFAs and depression.
383 **n-3 PUFAs status and depression.** Some workers have investigated levels of EFAs in
384 human tissue and possible correlation of these with depression. Most studies have
385 involved the analysis of fatty acid composition of phospholipids in plasma and red blood
386 cells; and while it is acknowledged that phospholipid composition in the brain is not
387 identical to serum, it is known that there are significant correlations between
388 phospholipid composition in blood and brain (Horrobin 2001).
389 In a review by Sontrop (2006) of published evidence linking n-3 PUFAs and depression,
390 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 post-mortem (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).

A clinical study investigating the efficacy of n-3 PUFAs for the treatment of depression during pregnancy also produced positive findings (Freeman *et al*., 2006). Fifteen pregnant women with MDD participated in this flexible-dose, open-label trial. Subjects started on 0.93g of EPA and DHA per day; the dose could be increased by 0.47g per day every 2 weeks to a maximum dose of 2.8g. 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. The earliest therapeutic trial of n-3 PUFAs in treating mood disorders, carried out in by Stoll *et al*., (1999), was seminal in its evidence of the 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). In fact the

findings were so robust that the trial was ended prematurely as it was deemed unethical to withhold treatment from the placebo group (Young and Martin 2003).

Three year after this study more encouraging 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

504 treatment group showed significantly decreased scores on the HDRS (P<0.001) compared
505 to the placebo group (Su 2003).
506 Despite these early results, not all of the earlier studies produced such positive outcomes.
507 Marangell *et al*., (2003) carried out a randomized, double-blind, placebo-controlled trial
508 of DHA monotherapy for patients with a major depressive episode. Thirty six patients
509 were randomly assigned to receive DHA dosage at 2g/day or placebo for 6 weeks. The
510 difference in response rates between the 2 groups did not reach statistical significance
511 and the trial failed to show a significant effect of DHA monotherapy in people with
512 MDD. The negative result in this study may reflect differing antidepressant effect of
513 DHA and EPA.
514 More recently, a small, randomized, controlled, double-blind pilot study of n-3 PUFA
515 treatment of childhood depression showed highly significant effects. 20 children between
516 the ages of 6- 12 years who had been depressed for an average of 3 months participated
517 in the study. They were randomly assigned to the treatment group or the placebo group.
518 Ratings were performed at baseline and at 2, 4, 8, 12 and 16 weeks using the Children's
519 Depression Rating Scale (CDRS), Children's Depression Inventory (CDI), and Clinical
520 Global Impression (CGI). The treatment group received 400mg EPA + 200mg DHA
521 daily. In the treatment group, 7 out of 10 children had a greater than 50% reduction in
522 CDRS scores compared to 0 out of 10 achieving greater than 50% reduction in CDRS
523 scores in the placebo group. Four out of 10 children in the n-3 PUFA group met the
524 remission criteria of a CDRS score <29 at study exit, while no subject in the placebo
525 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).

549 Further support for n-3 PUFAs as a prevention for psychotic disorders was also found in
550 a randomized, double-blind, placebo controlled trial conducted between 2004 and 2007
551 (Amminger *et al*., 2010). A 12-week intervention period of 1.2 g/day n-3 PUFA or
552 placebo was followed by a 40 week monitoring period. The total study of 12 months on
553 81 individuals at ultra-high risk of psychotic disorder concluded that n-3 PUFAs reduce
554 the risk of progression to psychotic disorder with significant reduction in positive
555 symptoms, negative symptoms, and general symptoms and improved functioning
556 compared with placebo (Amminger *et al*., 2010).
557 **Systematic review and meta-analyses.** Appleton *et al*., (2006) completed a systematic
558 review of published randomized, controlled trials investigating the effects of n-3 PUFAs
559 on depressed mood. Twelve trials to 2006 were included in a meta-analysis. The authors
560 concluded that the evidence examining the effects of n-3 PUFAs on depressed mood is
561 limited and difficult to summarize and evaluate because results vary considerably.
562 Appleton *et al*., (2010) subsequently presented an updated systematic review and meta-
563 analysis of the effects of n-3 long-chain PUFAs on depressed mood. Thirty five
564 randomized controlled trials were identified, 17 of which were not included in the
565 previous review. On this occasion, the authors concluded that while trial evidence of the
566 effects of n-3 on depressed mood has increased, it remains difficult to summarize because
567 of heterogeneity. The evidence suggests that there is some benefit of n-3 PUFAs in
568 individuals with diagnosed depressive illness but no evidence of any benefit in
569 individuals without a diagnosis of depressive illness (Appleton *et al*., 2010).
570 Another meta-analytic review of double-blind, placebo-controlled trials of antidepressant
571 efficacy of n-3 fatty acids included 10 studies with treatment lasting 4 weeks or longer. In

572 pooling the results of the 10 studies, the authors found a significant antidepressant effect
573 of n-3 PUFAs. Patients with clearly defined depression or bipolar disorder significantly
574 improved. Dose did not seem to change the antidepressant effect significantly (Lin and
575 Su 2007). Ross *et al*., (2007) critically reviewed the double blind placebo controlled
576 clinical trials published prior to April 2007 to determine whether n-3 PUFAs are
577 efficacious in a range of different psychiatric disorders. There was limited evidence in
578 schizophrenia, borderline personality disorder, and attention deficit disorder. The most
579 convincing evidence for the beneficial effects of n-3 PUFAs was found in mood
580 disorders. A meta-analysis of trials involving patients with MDD and bipolar disorder
581 provided evidence that n-3 PUFAs reduce symptoms of depression. It was suggested also
582 that treatment with EPA may be more beneficial in mood disorders that DHA, although
583 definite conclusions could not be made (Ross *et al*., 2007).
584 **Safety.** The overwhelming conclusion in the many studies reviewed is that PUFAs are
585 generally well tolerated by both children and adults with mild gastrointestinal effects
586 such as loose stools being the only consistently reported adverse event.
587 The US Department of Health and Human Services Agency for Healthcare Research and
588 Quality identified 148 n-3 PUFA studies that reported on adverse events in 20,000
589 subjects. Dosage was up to 6g/day fish oils. Gastrointestinal complaints were reported in
590 6.6% of the subjects taking n-3 PUFAs versus 4.3% in the placebo groups. Only one
591 study reported an increased incidence of bleeding while 77 studies reported no adverse
592 effects at all. The agency concluded that adverse effects of fish oils appear to be minor
593 while the Food & Drug Administration (FDA) has ruled that up to 3g/day of EPA + DHA
594 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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