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Role of Omega-3 Fatty Acids in the Etiology, Treatment, and Prevention of Depression: Current Status and Future Directions

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Abstract

Over the past three decades a body of translational evidence has implicated dietary deficiency in long-chain omega-3 (LC*n*-3) fatty acids, including eicosapenaenoic acid (EPA) and docosahexaenoic acid (DHA), in the pathophysiology and etiology of major depressive disorder (MDD). Cross-national and cross-sectional data suggest that greater habitual intake of preformed EPA+DHA is associated with reduced risk for developing depressive symptoms and syndromal MDD. Erythrocyte EPA and DHA composition is highly correlated with habitual fish or fish oil intake, and case-control studies have consistently observed lower erythrocyte EPA and/or DHA levels in patients with MDD. Low erythrocyte EPA+DHA composition may also be associated with increased risk for suicide and cardiovascular disease, two primary causes of excess premature mortality in MDD. While controversial, dietary EPA+DHA supplementation may have antidepressant properties and may augment the therapeutic efficacy of antidepressant medications. Neuroimaging and rodent neurodevelopmental studies further suggest that low LC*n*-3 fatty acid intake or biostatus can recapitulate central pathophysiological features associated with MDD. Prospective findings suggest that low LC*n*-3 fatty acid biostatus increases risk for depressive symptoms in part by augmenting pro-inflammatory responsivity. When taken collectively, these translational findings provide a strong empirical foundation in support of dietary LC*n*-3 fatty acid deficiency as a modifiable risk factor for MDD. This review provides an overview of this translational evidence and then discusses future directions including strategies to translate this evidence into routine clinical screening and treatment algorithms.

Keywords

Major depressive disorder; Long-chain omega-3 fatty acids; Eicosapentaenoic acid (EPA); Docosahexaenoic acid (DHA)

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Introduction

Major depressive disorder (MDD) is a leading cause of disability globally. In the United States (U.S.) severe forms of MDD are estimated to affect between 2-7% of the population and up to 16-20% suffer from milder forms (Kessler et al., 2007). The initial onset of MDD frequently occurs during adolescence and young adulthood (Kessler et al., 2005), and is ~2-fold more prevalent in females after puberty (Kessler, 2003). Outcomes data indicate that MDD is associated with excess premature mortality primarily attributable to suicide and cardiovascular-related disorders (Angst et al., 2002; Osby et al., 2001). Bipolar disorder is also associated with recurrent episodes of depression, and prodromal MDD is a risk factor for mania in at-risk youth (Axelson et al., 2015; Egeland et al., 2000; Howes et al., 2011). The first-line treatment for MDD in adolescents and adults is typically a selective serotonin reuptake inhibitor (SSRI). However, approximately 30-40 percent of adolescent MDD patients exhibit residual symptoms following standard SSRI treatment (Kennard et al., 2006; Emslie et al., 1997), and SSRI treatment may precipitate suicidality and mania in at-risk youth (Hammad et al., 2006; Martin et al., 2004; Strawn et al., 2014). These and other data highlight an urgent need to identify modifiable risk and resilience mechanisms associated with the etiology of MDD to inform improvements in treatment and ultimately prevention strategies.

While aggressive efforts have been devoted to the identification of genetic risk factors associated with psychiatric disorders including MDD, it has become apparent that both genetic and environmental factors confer vulnerability (Ehringer et al., 2006; Merikangas et al., 2002). For example, a meta-analysis of community-based twin studies of MDD yielded a heritability estimate of .37, indicating that approximately two thirds of the liability is attributable to environmental factors (Sullivan et al., 2000). Moreover, environmental factors can regulate gene expression through epigenetic effects (i.e., DNA methylation) independent of DNA sequence polymorphisms (Perroud et al., 2014; Zhang et al., 2013). Environmental factors can also interact with DNA polymorphisms to increase risk for developing psychiatric disorders (Caspi & Moffitt, 2006). Accordingly, aggressive efforts also need to be devoted to the identification of environmental risk factors, particularly in view of their amenability to modification and prevention.

Over the last three decades a body of translational evidence has emerged which suggests that the habitual diet is relevant to the etiology of MDD. Specifically, evidence has implicated dietary deficiency in essential long-chain omega-3 (LC*n*-3) fatty acids, including eicosapenaenoic acid (EPA) and docosahexaenoic acid (DHA), in the pathophysiology and etiology of MDD. This is supported by converging evidence from cross-national and cross-sectional epidemiological surveys, case-control LC*n*-3 fatty acid biostatus studies, prospective observational and LC*n*-3 fatty acid intervention studies, rodent neurodevelopmental studies, and recent neuroimaging findings. Additionally, accumulating evidence suggests that LC*n*-3 fatty acid deficiency may increase risk for suicide and cardiovascular disease, two primary causes of excess premature mortality in patients with MDD. This review provides an overview of translational evidence implicating LC*n*-3 fatty acid deficiency in the pathophysiology and etiology of MDD, and then discusses future

directions including strategies to translate this evidence into routine clinical screening and treatment algorithms.

LC*n*-3 fatty acid biosynthesis and biostatus

As background, omega-3 (*n*-3) and omega-6 (*n*-6) fatty acids are members of the polyunsaturated fatty acid (PUFA) family. Primary dietary sources of the short-chain *n*-3 fatty acid precursor α-linolenic acid (ALA, 18:3*n*-3) include flaxseed, linseed, canola, soy, and perilla oils, and primary dietary sources of the short-chain *n*-6 fatty acid precursor linoleic acid (18:2*n*-6) include safflower, soy, and corn oils. These PUFAs are considered 'essential' because mammals are entirely dependent on dietary sources to procure and maintain adequate concentrations in peripheral and central tissues. The biosynthesis of long-chain *n*-3 (LC*n*-3) fatty acids, including EPA (20:5*n*-3) and DHA (22:6*n*-3), from their short-chain precursors require a series of common and competitive microsomal desaturation and elongation reactions (Fig. 1)(Reardon & Brenna, 2013). The rate-limiting enzymes regulating LC-PUFA biosynthesis include delta-6 desaturase (delta6-desaturase, *FADS2*) and delta-5 desaturase (delta5-desaturase, *FADS1*), as well as elongases *(e.g., ELOVL5)*, and the final synthesis of DHA is catalyzed by β-oxidation within peroxisomes (Wanders, 2013). *FASD1* and *FADS2* genes are primarily expressed in the liver and brain and are co-localized to human chromosome 11q12-11q13.1 (Marquardt et al., 2000). Desaturase enzymes are regulated by several factors including gonadal hormones (Bakewell et al., 2006; Burdge & Wootten, 2002; Childs et al., 2010; Giltay et al., 2004; McNamara et al., 2009a), insulin (Brenner, 2003), as well as single nucleotide polymorphisms within *FADS2* and/or *FASD1* genes (Lattka et al., 2010). Recent evidence further suggests that epigenetic effects (*i.e.,* DNA methylation) are associated with delta5/6-desaturase enzyme activity (Howard et al., 2014) and that PUFA intake can induce DNA methylation resulting in reduced expression of *FADS2* and *ELOVL5* (Hoile et al., 2014). Therefore, PUFA homeostasis is ultimately governed by both environmental (i.e., diet) and genetic factors.

In healthy adult subjects ALA→EPA biosynthesis is extremely limited and ALA→DHA and EPA→DHA biosynthesis is negligible (Brenna et al., 2009). For example, 12-week supplementation with up to 3.6 g/d of flaxseed oil, a rich source of ALA, resulted in moderate increases in erythrocyte (red blood cell) EPA but did not significantly increase erythrocyte DHA levels in healthy adult subjects (Barcelo-Coblijn et al., 2008). Similarly, 4-week supplementation with flaxseed oil resulted in moderate increases in erythrocyte and breast milk EPA but did not significantly increase erythrocyte or breast milk DHA (Francois et al., 2003). This limitation in biosynthesis may be due in part to competition with high levels of linoleic acid (18:2*n*-6) in the diet (Taha et al., 2014). Unlike flaxseed oil, supplementation with fish oil robustly increases erythrocyte and breastmilk EPA+DHA biostatus (Flock et al., 2013; Arterburn et al., 2006; Barcelo-Coblijn et al., 2008). Primary sources of preformed LC*n*-3 fatty acids (EPA+DHA) include fatty cold water fish, including salmon, trout, tuna, as well as fish oil and algal-derived supplements. Accordingly, cross-national evidence has found that habitual fish intake is positively correlated with breastmilk (Brenna et al., 2007) and blood (Sands et al., 2005; Itomura et al., 2008) EPA+DHA composition. Together, these findings highlight the limited efficiency of hepatic PUFA

biosynthesis in healthy human subjects and suggest that LC*n*-3 fatty acid biostatus is highly dependent on the LC*n*-3 fatty acid composition of the habitual diet.

Relevance to depression

Epidemiology

Cross-national epidemiological surveys have observed a significant inverse correlation between per capita fish or seafood consumption (primary dietary sources of preformed EPA +DHA) and lifetime prevalence rates of MDD (Hibbeln, 1998; Peet, 2004), postpartum depression (Hibbeln et al., 2002), and bipolar spectrum disorders (Noaghiul & Hibbeln, 2003). Several cross-sectional studies have investigated the relationship between habitual fish or fish oil intake and depression rates in the general population. For example, a cross-sectional survey of 21,835 adult and elderly subjects from Norway found that subjects who ingested cod liver oil on a daily basis (EPA: ~300-600 mg/d; DHA: ~300-600 mg/d) were 30 percent less likely to have depressive symptoms than non-users after adjusting for multiple possible confounding factors (Raeder et al., 2007). A meta-analyses of thirteen cross-sectional studies found that higher intake of fish (as well as fruit, vegetables, and whole grains) was significantly associated with a reduced depression risk (Lai et al., 2014). Because the initial onset of MDD frequently occurs during adolescence, it is relevant that lower dietary LC*n*-3 fatty acid intake in adolescents is associated with elevated depressive symptoms as well as cardiovascular risk factors (Allen et al., 2013; Murakami et al., 2010; Oddy et al., 2011; O'Sullivan et al., 2011; Swenne et al., 2011). Although these findings provide indirect support for an inverse association between fish intake frequency and MDD prevalence, numerous cultural and genetic variables may also contribute to this association.

It has been estimated that there has been a sharp increase in the consumption of linoleic acid (18:2*n*-6), and a reciprocal decline in α-linolenic acid (18:3*n*-3) and LC*n*-3 fatty acids, in the U.S. over the last century (Blasbalg et al., 2011). While it is unclear whether this relative decline in LC*n*-3 fatty acids has been associated with a change in the prevalence rates of depression in the U.S., a retrospective study found that shifts away from fish-based to Western diets in Arctic communities was associated with increased rates of seasonal affective disorder, depression, suicide, and cardiovascular disease (McGrath-Hanna et al., 2003). Moreover, case-control studies find that patients with mood disorders are more likely to consume diets with lower amounts of LC*n*-3 fatty acids and ALA compared with healthy controls and/or recommended intake levels (Clayton et al., 2008; Edwards et al., 1998; Evans et al., 2014; Davison & Kaplan, 2012; Jacka et al., 2011). It is also relevant that MDD is associated with excess premature mortality primarily attributable to suicide and cardiovascular disease (Angst et al., 2002; Osby et al., 2001), and cross-sectional epidemiological evidence suggests that higher LC*n*-3 fatty acid intake may be protective against suicidality (Tanskanen et al., 2001) and cardiovascular disease (Whelton et al., 2004). Together these findings suggest that habitual diets containing lower amounts of LC*n*-3 fatty acids may increase risk for developing depressive symptoms, suicidality, and co-morbid cardiovascular disease.

LC*n*-3 fatty acid biosynthesis and biostatus

Extant evidence from genome-wide association studies does not support an association between polymorphisms in delta-6 (*FASD2*) and delta-5 desaturase (*FADS1*) genes in the etiology of MDD (Levinson, 2006). A recent genotyping study did not observe an association between common single-nucleotide polymorphisms in *FADS1* or *FASD2* genes and depression or suicidality (Sublette et al., 2015). However, DNA methylation in the *Elovl5* gene was found to be associated with depression and suicidality (Haghighi et al., 2015). Moreover, *FADS1* mRNA expression was significantly lower in the postmortem prefrontal cortex of MDD patients relative to controls, and there were trends for lower expression of *FADS2* and *ELOVL5* (McNamara & Liu, 2011). A microarray study similarly found that *FADS1* expression was reduced in postmortem prefrontal cortices of male MDD patients that committed suicide (Lalovic et al., 2010). It is also notable that antidepressant medications upregulate the expression of sterol regulatory element-binding protein (SREBP) (Raeder et al., 2006) which positively regulates *FADS1* and *FADS2* transcription (Matsuzaka et al., 2002). While these findings must be viewed as preliminary, they suggest that the dysregulation in LC*n*-3 fatty acid homeostasis in MDD may be mediated in part by epigenetic modifications of biosynthetic enzymes.

Several independent cross-sectional studies conducted in different countries have observed significantly lower erythrocyte membrane or plasma phospholipid EPA+DHA levels in adult MDD patients compared with healthy controls. A meta-analysis of 14 cross-sectional fatty acid composition studies found significant deficits in EPA and DHA, but not arachidonic acid (AA), in MDD patients (Lin et al., 2010). Other cross-sectional studies have similarly found that pediatric and adolescent patients with MDD exhibit erythrocyte EPA+DHA deficits compared with healthy youth (Clayton et al., 2008; Pottala et al., 2013; McNamara et al., 2014a). Some studies (Clayton et al., 2008; Adams et al., 1996; Edwards et al., 1998), but not others (Assies et al., 2010; Liu et al., 2013; McNamara et al., 2010a), have observed an inverse correlation between blood EPA+DHA levels, or a positive correlation between the AA/EPA ratio, and depression symptom severity. It is notable that erythrocyte EPA and/or DHA deficits are not unique to MDD, and have also been observed in patients with bipolar I disorder (McNamara & Welge, 2016), anxiety disorders (Green et al., 2006), and schizophrenia (van der Kemp et al., 2012). While there may be different etiological factors contributing to lower blood EPA+DHA levels observed in MDD patients, dietary fish oil supplementation, but not flaxseed oil supplementation (Gracious et al., 2010), is sufficient to robustly increase patient blood EPA+DHA levels (McNamara et al., 2014a). In view of evidence that erythrocyte EPA+DHA composition is highly correlated with habitual dietary fish intake and/or fish oil supplementation (Flock et al., 2013; Sands et al., 2005; Itomura et al., 2008), these data suggest that dietary EPA+DHA insufficiency represents a modifiable risk factor for EPA+DHA deficiency observed in MDD.

Several lines of evidence also suggest that increasing LC*n*-3 fatty acid status may reduce risk of suicide, a primary cause of excess premature mortality in MDD (Angst et al., 2002; Osby et al., 2001). A prospective longitudinal study found that low baseline plasma DHA composition was a significant predictor of future suicidal attempts in medication-free MDD patients (Sublette et al., 2006). In two case-control studies, erythrocyte or plasma LC*n*-3

fatty acid composition was found to be significantly reduced in suicidal patients (Garland et al., 2007; Huan et al., 2004). Two controlled trials found that dietary LC*n*-3 fatty acid supplementation reduced suicidality in MDD patients (Hallahan et al., 2007; Peet & Horrobin, 2002). However, prospective cohort studies have not observed an association between LC*n*-3 fatty acid intake and completed suicide in the general population (Tsai et al., 2014). Therefore, while extant evidence suggests that increasing LC*n*-3 fatty acid status in patients with psychiatric illness may be protective against suicidality, additional research is needed to evaluate whether depressed mood mediates this effect.

Excess premature mortality in patients with MDD is also attributable to cardiovascular-related diseases (Angst et al., 2002; Osby et al., 2001). Cross-sectional and prospective longitudinal studies suggest that low erythrocyte EPA+DHA ('omega-3 index') biostatus increases risk for cardiometabolic risk factors (Farzaneh-Far et al., 2009; Kelly et al., 2009; McKenney & Sica, 2007) and sudden cardiac arrest (Albert et al., 2002; Hu et al., 2002; Siscovick et al., 1995; Harris & Von Schacky, 2004). Moreover, LC*n*-3 fatty acid intake is associated with methylation of genes regulating immune-inflammatory and lipid homeostasis (Aslibekyan et al., 2014; Lee et al., 2013), and the low erythrocyte EPA+DHA levels observed in patients with MDD are associated with elevated serum levels of triglycerides and pro-inflammatory molecules including C-reactive protein (Baek & Park, 2013; Baghai et al., 2011). Additionally, the low erythrocyte EPA+DHA levels observed in patients with MDD are similar to levels observed in patients suffering acute coronary syndrome (Block et al., 2008) and would be anticipated to increase their risk for sudden cardiac arrest (Harris & Von Schacky, 2004)(Fig. 2). While the effects of LC*n*-3 fatty acid supplementation on cardiovascular events and sudden cardiac arrest in patients with a history of cardiovascular disease have been equivocal (Kwak et al., 2012), primary prevention studies in subjects without a history of cardiovascular disease (Wang et al., 2006) or subjects at high-risk for cardiovascular disease (Einvik et al., 2010) suggest that increasing LC*n*-3 fatty acid biostatus may have protective benefits. While there have been no LC*n*-3 fatty acid primary prevention studies conducted in patients with MDD, existing evidence provides a rationale for identifying and treating LC*n*-3 fatty acid deficiency in patients presenting with other cardiovascular risk factors.

The primary LC*n*-3 fatty acid found in mammalian brain gray matter is DHA, which comprises approximately 15% of total fatty acid composition (Carver et al., 2001; Connor et al., 1990; McNamara et al., 2008). Although EPA (20:5*n*-3) crosses the blood-brain barrier, it is rapidly oxidized and consequently comprises <1% of total brain fatty acid composition (Chen et al., 2013). In general human erythrocyte and frontal cortex DHA composition are positively correlated (Carver et al., 2001), and non-human primate studies indicate that DHA recuperation occurs more rapidly in erythrocytes than cortical gray matter following dietary fish oil supplementation (Connor et al., 1990). Case-control studies have investigated the fatty acid composition of postmortem brain tissue from MDD patients and/or suicide victims. These studies have observed DHA deficits in the prefrontal cortex or anterior cingulate of adult patients with MDD (Conklin et al., 2010; McNamara et al., 2007, 2013a), but not in the prefrontal cortex of adolescent or adult suicide victims (Lalovic et al., 2007; McNamara et al., 2009b). Other postmortem studies have not observed significant DHA deficits in temporal lobe structures including the amygdala in patients with MDD (Hamazaki

et al., 2012; McNamara et al., 2014b). While this evidence suggests that MDD may be associated with DHA deficits selective to prefrontal regions, in view of the limitations associated with the postmortem approach these findings should be viewed as preliminary (McNamara & Jandacek, 2010).

LC*n*-3 fatty acid supplementation studies

To date numerous small open-label or placebo-controlled studies have investigated the antidepressant effects of short-term LC*n*-3 fatty acid supplementation. Despite heterogeneity in study design in terms of daily dose, LC*n*-3 fatty acid intervention, EPA:DHA ratio, trial duration, concomitant medications, use of a bioactive placebo (i.e., olive oil), and baseline symptom severity, meta-analyses of controlled trials observed a significant, albeit modest, advantage of LC*n*-3 fatty acids over placebo for reducing depression symptom severity in patients with MDD (Appleton et al., 2015; Grosso et al., 2014; Mocking et al., 2016) or bipolar disorder (Sarris et al., 2012). Additional data suggests that interventions with a higher EPA to DHA ratio may have greater antidepressant efficacy (Sublette et al., 2011). Controlled and open-label trials have also found that LC*n*-3 fatty acid supplementation, administered either adjunctively or as monotherapy, significantly reduces depression symptom severity in pediatric and adolescent patients (Clayton et al., 2009b; McNamara et al., 2014a; Nemets et al., 2006; Wozniak et al., 2007). Controlled and open-label trials have also observed greater reductions in depressive symptoms by combining LC*n*-3 fatty acids with SSRI medications (Gertsik et al., 2012; Jazayeri et al., 2008; McNamara et al., 2014a; Peet & Horrobin, 2002). While this body of evidence suggests that dietary LC*n*-3 fatty acid supplementation may have acute ‘antidepressant’ effects, large-scale trials are warranted to confirm these findings.

In addition to acute antidepressant effects, emerging clinical evidence suggests that higher LC*n*-3 fatty acid status may be protective against the initial development of MDD. A prospective surveillance study found that lower baseline DHA levels were a significant predictor of depression development in human hepatitis C patients during treatment with the pro-inflammatory cytokine interferon-α (IFN-α)(Su et al., 2010). A second prospective surveillance study found that lower baseline DHA levels, or a higher baseline AA/EPA +DHA ratio, were significant predictors of depression development in initially non-depressed human hepatitis C patients during IFN-α treatment (Lotrich et al., 2013). It is notable that a higher baseline AA/EPA+DHA ratio was also associated with greater increases in the pro-inflammatory cytokine interleukin-6 (IL-6) during IFN-α treatment (Lotrich et al., 2013a). A controlled supplementation trial found that pretreatment with EPA alone, which increased both erythrocyte EPA and DHA levels, but not DHA alone decreased the incidence of depression during IFN-α treatment in hepatitis C patients (Su et al., 2014). In view of evidence that MDD patients exhibit elevated indices of peripheral (Dowlati et al., 2010) and central (Setiawan et al., 2015) inflammation, and LC*n*-3 fatty acids and their bioactive metabolites have anti-inflammatory and inflammation-resolving properties (Dalli et al., 2015; Groeger et al., 2010; Serhan, 2010), these prospective findings may have broader implications for understanding the role of low LC*n*-3 fatty acid biostatus and pro-inflammatory signaling cascades in the pathoetiology of MDD.

Neuroimaging studies

The initial onset of MDD frequently occurs during adolescence (Kessler et al., 2005), a developmental period associated with a sharp increase in frontal cortex DHA levels (Carver et al., 2001) and rapid and dynamic changes in frontal cortex functional and structural connectivity with limbic structures that regulate mood (Giedd et al., 1999, 2009; Paus et al., 1999). Youth and adults with MDD exhibit decreased frontal white matter integrity and reduced connectivity within frontal lobe cortical networks (Connolly et al., 2013; Dickstein et al., 2010; Ho et al., 2014). It is relevant, therefore, that recent neuroimaging studies found that perinatal *n*-3 fatty acid deficiency in monkeys (Grayson et al., 2014) or low erythrocyte DHA biostatus in typically developing children (Almeida et al., 2016) are associated with reduced functional connectivity within prefrontal cortical networks. Moreover, a recent intervention study found that fish oil supplementation increased white matter microstructural integrity in MDD patients in association with reductions in depression symptom severity (Chhetr et al., 2016). Furthermore, hippocampal grey matter volume deficits are among the most consistent and robust neurostructural abnormality observed in MDD (Kempton et al., 2011), and greater habitual dietary LC*n*-3 fatty acid intake (Conklin et al., 2007) and erythrocyte EPA+DHA composition (Pottala et al., 2014) are associated with larger hippocampal volumes among healthy adults. It is also notable that higher blood IL-6 levels were associated with smaller hippocampal grey matter volume among healthy adults (Marsland et al., 2008), and decreased corticostriatal functional connectivity in MDD patients (Felger et al., 2015). While additional research is required, these preliminary neuroimaging findings suggest that low EPA+DHA biostatus and associated increases in pro-inflammatory signaling may be linked with abnormalities in cortical structure and function implicated in MDD.

Rodent studies

Animal studies have provided critical insight into the role of dietary LC*n*-3 fatty acids in normal brain development. The advantage of animal feeding studies is the ability to systematically and selectively control *n*-3 fatty acid intake during development, and perform invasive investigations of brain neurochemistry, neuroanatomy, and/or gene expression. In general, feeding studies have demonstrated that brain DHA accrual during perinatal development is required for normal cortical neurogenesis (Beltz et al., 2003; Coti Bertrand et al., 2006; Kawakita et al., 2006), neuroblast migration (Yavin et al., 2009), neuronal differentiation and arborization (Calderon & Kim, 2004), neurotrophic factor expression (Ikemoto et al., 2000; Rao et al., 2007), nerve growth factor-induced neurite outgrowth and synaptogenesis (Cao et al., 2009; Innis et al., 2001), and synaptic pruning (de Velasco et al., 2012). Additionally, LC*n*-3 fatty acids deficiency during development is associated with systemic inflammation (Madore et al., 2014; McNamara et al., 2010b), and increased vulnerability to neurodegenerative processes associated with inflammation (Orr et al., 2013) and lipid peroxidation (Green et al., 2001; Yavin et al., 2002). These and other data suggest that there are optimal LC*n*-3 fatty acids levels required for normal brain maturation and resilience.

Additional evidence from animal studies suggests that deficits in dietary LC*n*-3 fatty acids during perinatal brain development significantly impacts neurotransmitter systems implicated in MDD including serotonin (5-hydroxytryptamine, 5-HT) and dopamine. Maternal dietary fish oil fortification significantly increases serotonin concentrations in the frontal cortex (Chalon et al., 1998) and attenuates reductions in frontal cortex serotonin content in response to chronic stress (Vancassel et al., 2008) in young adulthood. Conversely, perinatal deficits in cortical DHA accrual are associated with impaired fenfluramine-induced elevations in serotonin release which are reversible with early (P0-P14), but not later (P21), postnatal *n*-3 fatty acid supplementation (Kodas et al., 2004). Perinatal deficits in cortical DHA accrual are also associated with reductions in midbrain expression of tryptophan hydroxylase-2, the rate-limiting enzyme in serotonin biosynthesis (McNamara et al., 2009c), and elevations in 5-HT_{2A} receptor binding density in the rat frontal cortex (Delion et al., 1996). The 5-HIAA/5-HT ratio, an index of serotonin turnover, is significantly elevated in the regional brain of adult rats fed n-3-deficient diets, and this increase was positively correlated with plasma IL-6 levels and prevented by early normalization of *n*-3 fatty acid status (McNamara et al., 2010). Importantly, the increase in the 5-HIAA/5-HT ratio observed in the perinatal DHA-deficient rat brain is opposite to that produced by the SSRI antidepressant fluoxetine (McNamara et al., 2013b). Together this evidence suggests that LC*n*-3 fatty acid status during development has an enduring impact on central serotonin neurotransmission in young adult rats.

Consistent with clinical evidence implicating a dysregulation in serotonin neurotransmission in the pathophysiology of depression and aggression (Arango et al., 2002; Coccaro et al., 1997), post-weaning deficits in cortical DHA accrual are associated with elevated behavioral indices of depression and aggression in rats (DeMar et al., 2006). Importantly, dietary fish oil fortification significantly decreases depression-like behavior similar to SSRI medications in the forced swimming test, an effect that may be mediated by changes in 5-HT_{1A} receptor function (Carlezon et al., 2005; Huang et al., 2008; Vines et al., 2012). Combining dietary fish oil supplementation with fluoxetine is significantly more effective than fluoxetine alone for reducing depression-like behavior in the forced swim test (Laino et al., 2010; Lakhwani et al., 2007). Although post-weaning deficits in cortical DHA accrual are not associated with diminished SSRI efficacy in female rats in the forced swim test (McNamara et al., 2013b), it is associated with abnormal behavioral activation in male rats (Able et al., 2014). It is also relevant that the Flinders Sensitive Line rats, an inbred rat model of depression, exhibit constitutive increases in regional brain AA/DHA ratio (Green et al., 2005). Together these findings suggest that DHA biostatus is associated with serotonin-regulated behaviors including depression and aggression, and that fish oil supplementation has antidepressant-like effects similar to SSRI medications.

A deficit in mesolimbic dopamine neurotransmission has been implicated in anhedonia, a core feature of depression (Nestler & Carlezon, 2006; Stein, 2008). Rat studies have demonstrated that deficits in brain DHA accrual during perinatal development are associated with a significant loss of dopamine neurons in the ventral tegmental area, the source of mesolimbic and mesocortical dopamine projections (Ahmad et al., 2008). Perinatal deficits in brain DHA accrual is associated with enduring deficits in mesocortical and mesolimbic dopamine neurotransmission in young adult rats that are reversible with early (P0-P14), but

not later (P21), postnatal *n*-3 fatty acid supplementation (Kodas et al., 2002 Zimmer et al., 1998, 2002). Adolescent rats subjected to perinatal deficits in brain DHA accrual also exhibit increased expression of tyrosine hydroxylase, the rate limiting enzyme in dopamine biosynthesis, in the dorsal striatum (Bondi et al., 2014). Maternal dietary fish oil supplementation throughout gestation and lactation significantly increases dopamine concentrations in the frontal cortex of adult offspring (Chalon et al., 1998). These findings suggest that early perinatal brain DHA accrual is critical for the functional maturation of mesocortical and mesolimbic dopamine systems.

Future Directions – Clinical implementation

Together the reviewed body of translational evidence strongly suggests that LC*n*-3 fatty acid deficiency, particularly during perinatal development, may represent a plausible and modifiable risk factor for MDD. Among the clinical findings, meta-analyses of independent case-control studies demonstrate that MDD patients exhibit significantly lower blood EPA and/or DHA levels, which are correlated with fish or fish oil intake, compared with demographically similar healthy controls. Additionally, cross-sectional evidence and meta-analyses of controlled fish oil intervention studies suggest that increasing EPA+DHA biostatus mitigates risk for depressive symptoms, and potentially suicidality and cardiovascular disease. Therefore, translating this evidence into clinical practice by implementing routine screening and treatment of low blood EPA+DHA levels in patients with MDD represents an important future direction. Below we briefly discuss existing resources and general guidelines required for routine screening and treatment of low blood EPA+DHA levels in clinical practice.

Screening for LC*n*-3 fatty acid deficiency

There are currently several laboratory facilities that routinely perform blood fatty acid analyses by gas-liquid chromatography. For example, OmegaQuant, LLC is a Clinical Laboratory Improvement Amendments (CLIA)-certified lab that specializes in determining the blood fatty acid composition (www.omegaquant.com). For this procedure, whole blood (~25 uL) is obtained from a finger prick and is spotted and dried onto anti-oxidant treated card which is then shipped at ambient temperature. Analogous to routine cholesterol testing, this approach can provide a valid, reliable, and relatively non-invasive measure of a patient's EPA+DHA biostatus. Erythrocyte EPA+DHA composition (‘omega-3 index’) has been widely characterized as a risk biomarker in the context of coronary heart disease (Harris, 2008). Based in part on prospective longitudinal evidence, erythrocyte EPA+DHA composition of ≤4% of total fatty acid composition is thought to place one at ‘high risk’ for sudden cardiac death, whereas >8% is protective (Harris & Von Schacky, 2004). Because MDD is associated with excess premature mortality attributable in part to cardiovascular-related diseases (Angst et al., 2002; Osby et al., 2001), and the erythrocyte EPA+DHA deficits consistently observed in MDD patients (Lin et al., 2010) are similar to patients suffering acute coronary syndrome (Block et al., 2008)(Fig. 1), the same risk categories may be appropriate within the context of clinical practice. It is also notable that erythrocyte EPA +DHA composition of ≤4% is highly prevalent in youth with MDD, and may therefore aid in the identification of youth that may be at elevated risk for developing MDD. For example,

our study found that 90 percent of adolescents with SSRI-resistant MDD exhibited erythrocyte EPA+DHA composition of ≤4% (McNamara et al., 2014a). Collectively, these data support the idea that erythrocyte or whole blood EPA+DHA composition of ≤4% can be considered to be a 'state of deficiency' that requires corrective intervention.

Treating LC*n*-3 fatty acid deficiency

The U.S. Food and Drug Administration (FDA) considers LC*n*-3 fatty acid doses up to 3 g/d to be 'generally regarded as safe', and the European Food Safety Authority (EFSA) considers doses up to 5 g/d to be safe. The American Psychiatric Association has adopted the consensus recommendations of the American Heart Association for an EPA+DHA dose of 1 g/d in patients with MDD (Freeman et al., 2006). The American Heart Association also recommends 3 g/d EPA+DHA for reducing elevated triglyceride levels. Prescription ethyl ester EPA+DHA (Lovaza® in the US, Omacor® in Europe, GlaxoSmithKline), purified ethyl ester EPA containing no DHA (Vascepa®, Amarin Corporation), and a free versus ethyl ester EPA+DHA formulation (Epanova®, AstraZeneca) have been approved by the U.S. FDA for the treatment of hypertriglyceridemia (≥500 mg/dL). More recently a generic version of Lovaza has become available (Teva Pharmaceuticals USA, Inc.). Over-the-counter fish oil supplements containing similar ethyl ester EPA+DHA concentrations are also widely available. It is important to note, however, that no LC*n*-3 fatty acid formulation is currently approved by the FDA for the treatment of any psychiatric disorder, and reimbursement for off-label use is ultimately at the discretion of the insurance provider.

Controlled intervention studies suggest that daily EPA+DHA doses of 1-2 g are sufficient to increase erythrocyte EPA+DHA composition to levels ≥4% (Flock et al., 2013). EPA+DHA doses in the range of 1-4 g/d in a 2:1 EPA to DHA ratio are efficacious for the treatment of depressive symptoms (Grosso et al., 2014; Sublette et al., 2011). Lower initial starting doses may be appropriate for children. For example, a daily dose of 600 mg fish oil monotherapy significantly reduced depression symptom severity in children with MDD (Nemets et al., 2006). As with other psychotropic medications, upward dose titration may be required as clinically indicated. For example, in an open-label flexible dosing study LC*n*-3 fatty acid monotherapy led to a statistically significant reduction in depression (and manic) symptom severity scores in pediatric bipolar patients (Wozniak et al., 2007). In this study the starting dose was 1.3 g/d of EPA+DHA, the maximum dose was 4.3 g/d, and the mean dose was 2.6 g/d. While there is a need for additional dose-titrating secondary prevention trials to elucidate optimal LC*n*-3 fatty acid dosing strategies, existing evidence suggests that a 1 g/d starting dose of EPA+DHA is safe and well-tolerated in pediatric, adolescent, and adult psychiatric patients.

Fish oil and LC*n*-3 fatty acids have an established long-term safety record in the general population. Potential adverse events associated with LC*n*-3 fatty acid supplementation include gastrointestinal disturbances, including nausea, diarrhea, gastroesophageal reflux, eructation, and less commonly emesis. In double-blind clinical trials of adult patients, the principal adverse events reported after chronic (8-12 weeks) treatment were gastrointestinal problems, and were considered mild and reported as frequently in patients receiving the placebo (Freeman et al., 2006). In studies conducted in pediatric and adolescent patients, no

clinically-significant treatment-emergent adverse events were reported at doses up to 4.3 g/d (Clayton et al., 2009; Nemets et al., 2006; Wozniak et al., 2007). In adults, treatment with LC*n*-3 fatty acid doses up to 7.5 g/d for 6 months were found to be well-tolerated (Yee et al., 2010).To minimize the gastrointestinal adverse events associated with LC*n*-3 fatty acids, patients should be instructed to take their capsules with meals. Although taking fish oil at high doses (>3 g/d) has been associated in isolated cases with increased bleeding time in subjects also taking anticoagulant medications (Buckley et al., 2004), controlled clinical trials have found that chronic high dose EPA+DHA alone or in combination with aspirin does not increase risk for clinically-significant increases in bleeding time (Eritsland et al., 1995; Mueller et al., 1992; Harris, 2007). Another safety consideration involves the potential threat of contamination of fish and seafood with methyl mercury, PCBs, and other environmental pollutants. However, most over-the-counter fish oil supplements are highly purified and cannot exceed U.S. FDA limits for PCBs. As with all medications, patients should be informed of potential risks associated with LC*n*-3 fatty acids, and patients with an allergy to shellfish or seafood should be closely monitored.

Conclusions

Major advances in the treatment and prevention of MDD will be accelerated by the identification of modifiable pathogenic factors conferring vulnerability. Evidence emerging over the past three decades suggests that habitual dietary LC*n*-3 fatty acid insufficiency, particularly during perinatal development, may represent a modifiable risk factor for MDD. Cross-sectional fatty acid composition studies provide strong evidence that adolescent and adult patients with MDD exhibit significant blood LC*n*-3 fatty acid deficits compared with healthy controls. Dietary supplementation with fish oil is sufficient to correct blood LC*n*-3 fatty acid deficits in MDD patients, and controlled trials suggest that LC*n*-3 fatty acid supplementation may reduce depressive symptoms in MDD patients. While controversial, evidence also suggests that LC*n*-3 fatty acid deficiency may increase risk for suicide and cardiovascular disease, two principle causes of excess premature mortality in patients with MDD. Recent prospective evidence further suggests that higher peripheral LC*n*-3 fatty acid status is protective against the initial development of MDD in response to inflammation, and suggest that low LC*n*-3 fatty acid biostatus may increase risk for depressive symptoms by augmenting pro-inflammatory responsivity. Additionally, neuroimaging and rodent neurodevelopmental studies provide evidence that LC*n*-3 fatty acid insufficiency impacts brain development in a manner relevant to the pathophysiology and treatment of MDD. When taken collectively, these translational findings provide a strong empirical foundation in support of dietary LC*n*-3 fatty acid deficiency being a modifiable risk factor for MDD.

While this body of evidence provides a compelling rationale to screen and treat LC*n*-3 fatty acid deficiency in patients with MDD, it has been slow impact conventional psychiatric training and practice. This may be due in part to a general lack of nutritional training in psychiatry, though the field is slowing evolving and nutritional medicine is gaining credibility (Sarris et al., 2015). While several independent meta-analysis have found that LC*n*-3 fatty acids are efficacious for reducing depression symptom severity antidepressant, it is important to recognize that neurostructural and neurochemical perturbations resulting from LC*n*-3 fatty acid deficiency during development may not be reversible with short-term

treatment. This is directly supported by rodent studies finding that enduring impairments in serotonin and dopamine neurotransmission resulting from perinatal *n*-3 fatty acid deficiency are reversible with early but not later *n*-3 fatty acid supplementation despite normalization of LC*n*-3 fatty acid biostatus. Therefore, early detection and treatment of LC*n*-3 fatty acid deficiency may be required to exert maximal protection against the initial development of MDD. Indeed, because LC*n*-3 fatty acid *monotherapy* is safe and well-tolerated it is ideally suited as a prodromal intervention for youth at increased risk for developing MDD. This approach is supported by the observation that fish oil supplementation prevented or delayed the onset of psychosis in ultra-high risk youth (Amminger et al., 2010, 2015). Additionally, within a 'clinical staging' framework LC*n*-3 fatty acid *monotherapy* would also represent a safe first-line intervention in youth with MDD, particularly those at risk for SSRI-associated adverse events.

While there is a need for additional research to optimize and standardize LC*n*-3 fatty acid screening and treatment approaches, current evidence and existing infrastructure support widespread implementation in psychiatric practice. As proof-of-concept, our group recently initiated a pilot program that routinely performs blood fatty acid testing in all patients admitted to an in-patient psychiatric clinic in suburban Cincinnati (Messamore & McNamara, 2016). To date we have performed whole blood fatty acid tests on over one hundred patients with different psychiatric disorders, including MDD. Consistent with prior cross-sectional studies, initial results suggest that the majority of patients exhibit whole blood EPA+DHA levels at ≤4. In several notable cases, treating EPA+DHA deficiency with either prescription or over-the-counter fish oil supplements resulted in remarkable and sustained improvements in mood symptoms. Although these data must be viewed as preliminary, they demonstrate the feasibility of implementing routine screening and treatment of EPA+DHA deficiency in psychiatric practice.

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Highlights

- A body of translational evidence suggests that dietary long-chain omega-3 (LC*n*-3) fatty acid deficiency, particularly during development, is a modifiable risk factor for depression.
- LC*n*-3 fatty acid deficiency is also a potential risk factor for suicide and cardiovascular disease, two primary causes of excess premature mortality in patients with MDD.
- Low LC*n*-3 fatty acid biostatus may increase risk for depressive symptoms by augmenting pro-inflammatory signalling.
- Future directions include implementing routine screening and treatment of LC*n*-3 fatty acid deficiency in clinical practice.

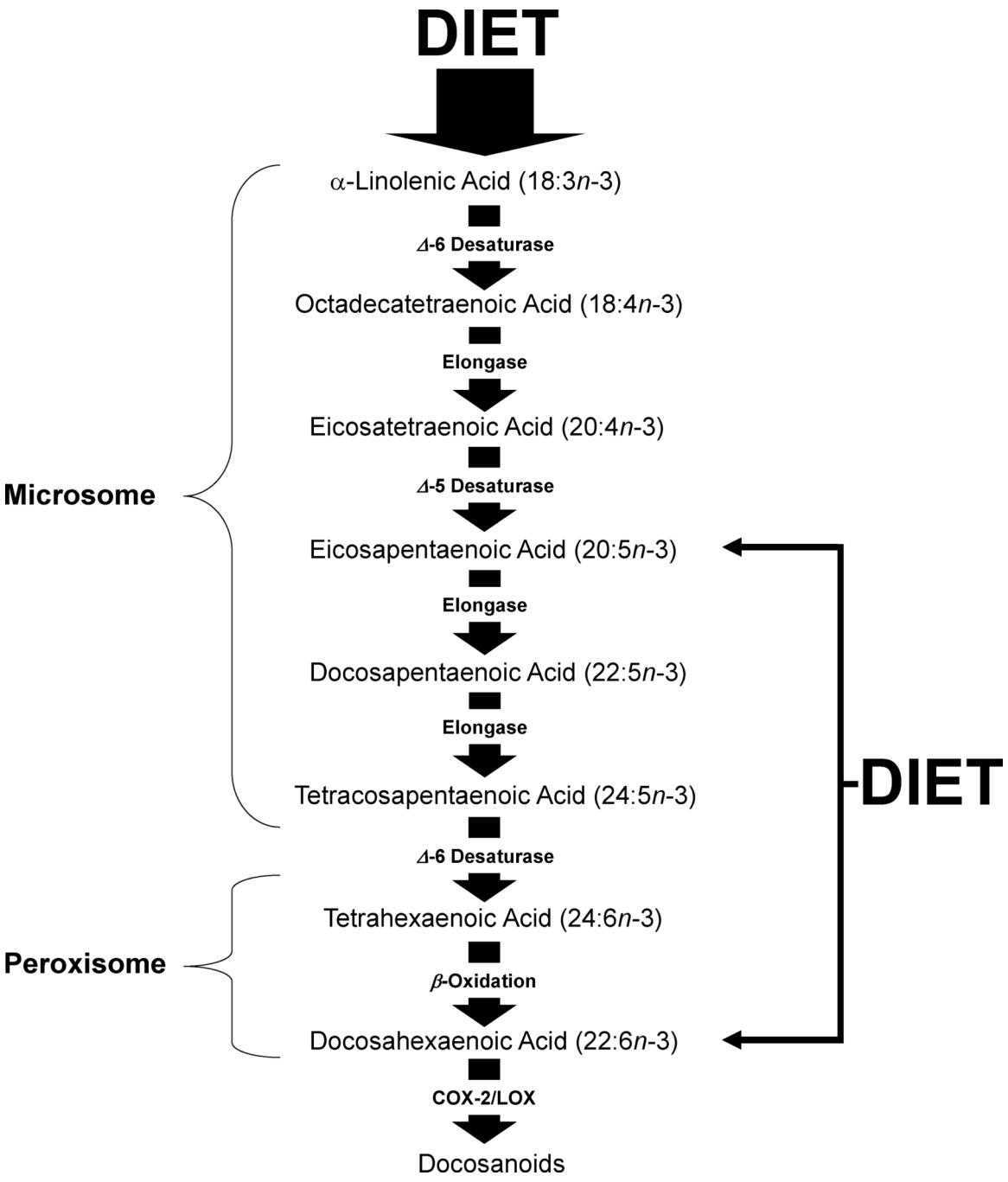

Figure 1.

Diagram illustrating the biosynthetic pathway of omega-3 fatty acids. The biosynthesis of docosahexaenoic acid (DHA, 22:6*n*-3) from dietary α-linolenic acid (18:3*n*-3) requires a series of microsomal elongation (*ELOVL5*) and delta-5 (*FADS1*) and delta-6 desaturase (*FADS2*) mediated reactions. The final synthesis of DHA is catalyzed by β-oxidation within peroxisomes. Metabolism of DHA yields inflammation-resolving docosanoids. Preformed DHA and EPA can also be obtained directly from the diet.

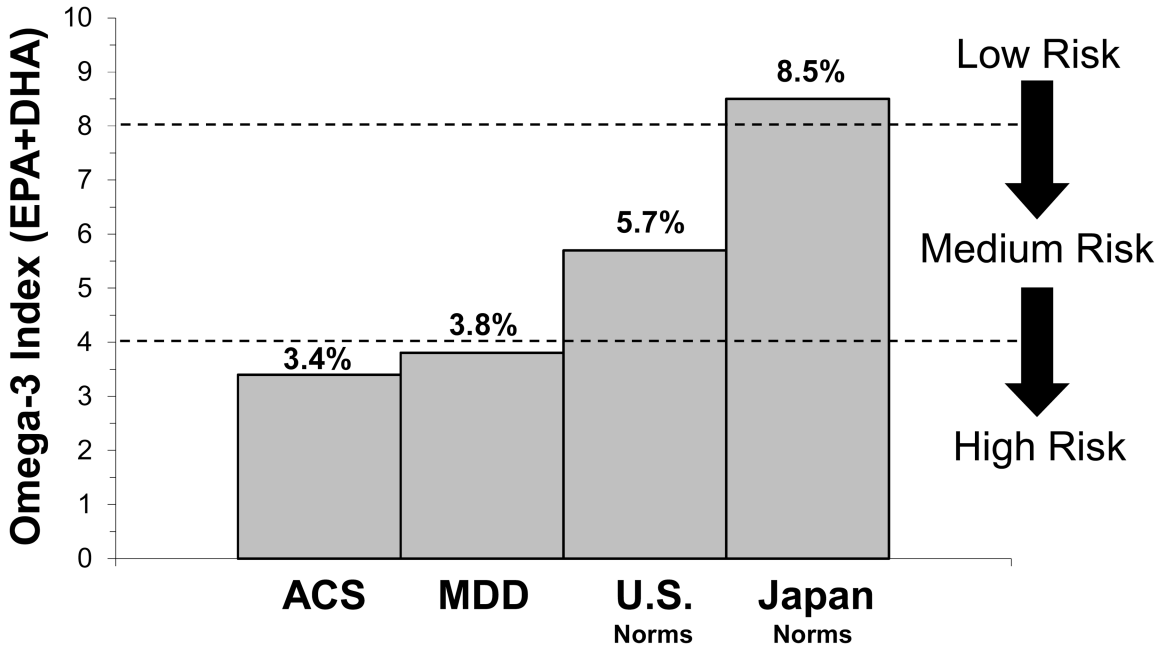

Figure 2.

Comparison of the mean erythrocyte 'omega-3 index' (EPA+DHA composition) in adult patients with acute coronary syndrome (ACS) residing in the U.S. (*n*=768)(Block et al., 2008), adult patients with MDD residing in the Chicago area (*n*=20)(McNamara et al., 2010a), normative values from a cohort of subjects residing in the U.S. (*n*=11,329, http://www.omegaquant.com/fatty-acids-regularly-measured/), and adults residing in Japan (*n*=456)(Itomura et al., 2008). Proposed 'risk zones' for sudden cardiac death derived from prospective longitudinal studies are indicated (Harris & Von Schacky, 2004). Note that MDD patients exhibit an 'omega-3 index' that is similar to patients with ACS, and places them at 'high risk' for sudden cardiac arrest. In view of evidence implicating both EPA and DHA deficiency in the pathophysiology of MDD, it is proposed that similar 'risk zones' be adopted in psychiatric practice to identify patients requiring corrective supplementation. Controlled intervention studies suggest that daily EPA+DHA doses of 1-2 g are sufficient to increase erythrocyte EPA+DHA composition to levels ≥4% (Flock et al., 2013).