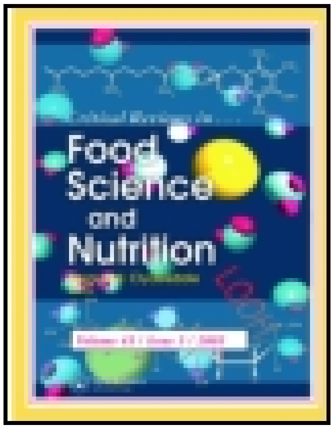

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The Role of Nutrients in Protecting Mitochondrial Function and Neurotransmitter Signaling: Implications for the Treatment of Depression, PTSD, and Suicidal Behaviors

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The Role of Nutrients in Protecting Mitochondrial Function and Neurotransmitter Signaling: Implications for the Treatment of Depression, PTSD, and Suicidal Behaviors

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ABSTRACT

Numerous studies have linked severe stress to the development of major depressive disorder (MDD), and suicidal behaviors. Furthermore, recent preclinical studies from our laboratory and others have demonstrated that in rodents, chronic stress and the stress hormone cortisol has caused oxidative damage to mitochondrial function and membrane lipids in the brain. Mitochondria play a key role in synaptic neurotransmitter signaling by providing adenosine triphosphate (ATP), mediating lipid and protein synthesis, buffering intracellular calcium, and regulating apoptotic and resilience pathways. Membrane lipids are similarly essential to central nervous system (CNS) function, because cholesterol, polyunsaturated fatty acids, and sphingolipids form a lipid raft region, a special lipid region on the membrane that mediates neurotransmitter signaling through G-protein coupled receptors and ion channels. Low serum cholesterol levels, low antioxidant capacity, and abnormal early morning cortisol levels are biomarkers consistently associated with both depression and suicidal behaviors. In this review, we summarize the manner in which nutrients can protect against oxidative damage to mitochondria and lipids in the neuronal circuits associated with cognitive and affective behaviors.

These nutrients include ω3 fatty acids, antioxidants (vitamin C and zinc), members of the vitamin B family (Vitamin B12 and folic acid) and magnesium. Accumulating data have shown that these nutrients can enhance neurocognitive function, and may have therapeutic benefits for depression and suicidal behaviors. A growing body of studies suggests the intriguing possibility that regular consumption of these nutrients may help prevent the onset of mood disorders and suicidal behaviors in vulnerable individuals, or significantly augment the therapeutic effect of available antidepressants. These findings have important implications for the health of both military and civilian populations.

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INTRODUCTION

Chronic severe stress has been directly implicated in the pathogenesis of depression (Charney and Manji, 2004), and suicidal behaviors (Robinson *et al.*, 2009). In United States (US) military populations, the suicide rate has been found to correlate with the frequency of deployment, suggesting that the prolonged exposure to stress levels may play a role (Bryan, 2010). Historically, suicide rates for active duty military personnel in the US and in other industrialized countries were lower than suicide rates for the general population—usually less than half (Rothberg *et al.*, 1990). However, studies over the last decade have described rising suicide rates in the US military populations (Lineberry, 2009), a finding that has lent increasing urgency to both military and civilian efforts at suicide prevention.

It has been well-established that the hypothalamic-pituitary-adrenal (HPA) axis is activated during stress, with increased levels of the stress hormone cortisol. For instance, cortisol serum levels are elevated in many depressed patients, and the dexamethasone suppression test (DST) did not inhibit serum cortisol levels (Sher, 2007). Patients with Cushing's disease, which is characterized by high cortisol levels, commonly develop depressive symptoms (Wolkowitz *et al.*, 2001). Altered morning cortisol levels have also been noted in individuals who attempted suicide (Sher, 2007). Moreover, it is noteworthy that "depression" in the sense of a low mood is a symptom of many vitamin/mineral deficiencies (e.g. Folic acid, vitamin C, magnesium.) (Bourre, 2004). Therefore, it is important to prevent depressive episodes due to vitamin/mineral deficiency, particularly for people under high levels of stress. The role of nutrients in the treatment of depression and suicidal behaviors has been extensively studied in the civilian population (Cocchi *et al.*, 1980, Papakostas *et al.*, 2005, Enya *et al.*, 2004, Li and Zhang, 2007, Sowa-Kucma *et al.*, 2008). Whether or not the nutrients may help as a strategy for the prevention or adjunctive treatment of depression or suicidal ideation in the military and civilian population remains underexplored.

Recent preclinical and clinical studies have shown that chronic severe stress causes oxidative damage to mitochondrial function and to membrane lipids, resulting in aberrant neurotransmitter signaling and information processing in synapses and circuits mediating affective, cognitive, motoric, and neurovegetative behaviors (Shelton, 2007). We begin this review by describing the relevant evidence linking disrupted mitochondrial function, membrane lipids, and neurotransmitter signaling with depression, and suicidal behaviors. We then summarize the clinical research data demonstrating that specific nutrients that act to protect mitochondria and neurotransmitter signaling are involved in the pathogenesis and treatment of these disorders. These nutrients include ω3 fatty acids, antioxidants, B family vitamins, and magnesium. Finally, we discuss the preclinical and clinical evidence that regular use of these nutrients may have preventive effects in the treatment of depression or suicidal behavior.

STRESS AND SLEEP DEPRIVATION CAUSE OXIDATIVE DAMAGE TO MITOCHONDRIAL FUNCTION AND LIPID COMPOSITION, LEADING TO IMPAIRED NEUROTRANSMITTER SIGNALING

Stress and altered HPA axis activity have been shown to increase oxidative damage and reduce antioxidant defense (Epel, 2009, Irie *et al.*, 2005, McIntosh and Sapolsky, 1996, Wolkowitz *et al.*, 2008). Oxidative stress occurs when the production of oxygen-free radicals exceeds the capacity of antioxidants to neutralize them (McIntosh and Sapolsky, 1996). After chronic severe stress, *in vivo* glutathione (GSH, decrease of which is an indicator for oxidative stress) levels were found to be depleted, suggesting a state of oxidative stress (Madrigal *et al.*, 2001). The study further noted that mitochondrial function was also reduced after chronic stress. Inhibiting GSH depletion by aminoguanidine (a nitric oxide synthase inhibitor) protected against the mitochondrial dysfunction induced by chronic stress (Madrigal *et al.*, 2001). In addition, lipids in the brain are particularly vulnerable to oxidative stress, which has been found to induce lipid peroxidation, and leads to degradation of polyunsaturated fatty acids (PUFAs) (Arts *et al.*, 2007, Virmani *et al.*, 2005). Taken together, the evidence suggests that oxidative damage induced by chronic stress may cause mitochondrial dysfunction and reduce lipid production (including PUFAs).

Accumulating research also shows that sleep deprivation is a neurobiological stressor that causes oxidative damage in the brain (Lavie, 2009, McEwen, 2006). Other studies demonstrated that antioxidant capacity was decreased in peripheral tissues after sleep deprivation (Everson *et al.*, 2005).Indeed, it has been proposed that one of the biological functions of sleep may be to protect against oxidative stress (Wolf *et al.*, 2007). There is extensive and well-known literature on long-term disrupted sleep cycles as a precipitant for mood disorders (Wirz-Justice, 2006), and given the disrupted sleep cycle that many soldiers and trainees experience (e.g., during basic training, deployment, or military missions), this stressor may be of particular importance in military populations (van Liempt *et al.*, 2006).

Oxidative stress, homocysteine (a neurotoxin for mitochondrial function) increases, and glucocorticoid receptor trafficking all affect mitochondrial function during chronic stress. High ROS (superoxide, hydrogen peroxide, and hydroxyl radical) levels damage mitochondrial function (Jou *et al.*, 2009, Madrigal *et al.*, 2001, Sorce and Krause, 2009). It has been shown that p66Shc is a proapoptotic protein involved in ROS production in mitochondria leading to mitochondrial damage and apoptosis under oxidative or genotoxic stress conditions such as H_2O_2 or UV exposure. (Calabrese V, *et al.*, 2010). Moreover, in both acute and chronic stress animal models, the homocystenine levels were significantly increased (Black and Garbutt, 2002, de Souza *et al.*, 2006, Taqliari *et al.*, 2010). The molecular mechanism(s) for homocysteine increase induced by the chronic stress remains unclear. Notably, some studies have suggested a link between high homocysteine concentrations and increased risk of depression (Almeida *et al.*, 2004, Almeida *et al.*, 2008). Recent studies have similarly shown that the stress hormone corticosterone directly modulates mitochondrial function (Du *et al.*, 2009). While brief increase of corticosterone enhanced mitochondrial function, high doses or long-term administration decreased levels of the glucocorticoid receptor and neuroprotective molecule B-cell lymphoma 2 (Bcl-2) in mitochondria. Similar results were found in rats exposed to a chronic stress paradigm (Du *et al.*, 2009).

Mitochondria are key regulators of neurotransmitter signaling at dendrites and synapses. They mediate important and diverse cellular functions in the central nervous system (CNS), including adenosine triphosphate (ATP) production, synaptic protein expression, lipid synthesis, intracellular calcium buffering, resilience, and apoptosis (Quiroz *et al.*, 2008, Zundorf and Reiser,2011). Especially in remote axons, dendrites, and synapses, mitochondria function as a “local government” to synthesize energy ATP, lipids, and proteins; provide substrates for lipid synthesis; maintain calcium homeostasis; and modulate apoptotic pathways to determine resilience and atrophy (Quiroz *et al.*, 2008, Zundorf and Reiser,2011). Cumulative evidence further shows that mitochondria are a key regulator of neurotransmitter signaling at the synapses (Ben-Shachar and Laifenfeld, 2004, Verstreken *et al.*, 2005) and, in conjunction with synaptic calcium dynamics, play a very active role in regulating synaptic plasticity (Ben-Shachar and Laifenfeld, 2004, Brenner-Lavie *et al.*, 2009, Mattson *et al.*, 2008, Verstreken *et al.*, 2005). For instance, mitochondrial transport is significantly increased in response to neuronal activity and is essential for enhancing synaptic strength (Mattson, 2007, Verstreken *et al.*, 2005). In support of these findings, it has been suggested that the atrophy of hippocampal dendrites and synapses seen in response to chronic stress may be due to decreased mitochondrial function (Cook and Wellman, 2004, Pavlides *et al.*, 2002).

Lipids are similarly particularly vulnerable to oxidative damage (Arts *et al.*, 2007). Sixty percent of the wet weight of the mammalian brain comprises lipids. Approximately 70% of the fatty acid pool is made de novo, and 30% must be obtained through diet. Seafood, fish oils, and fortified foods are rich sources of ω–3 polyunsatuated fatty acids (ω–3 PUFAs: eicosapentaenoic acid (EPA), docosapentaenoic acid (DPAω–3), and docosahexaenoic acid (DHA)), as well as cholesterol. DHA comprises 14% of total fatty acids in the body and is concentrated in neuronal membranes and synapses (Brunner *et al.*, 2002, Kunugi, 2001). The composition of lipids, including cholesterol and PUFAs, can be affected by both cellular function and diet. In this regard, oxidative stress has a large impact on lipid metabolism (including both cholesterol and PUFAs). Lipid peroxidation leads to oxidative lipid deterioration, which alters membrane permeability and fluidity and results in lipid degradation (Delibas *et al.*, 2004, Engstrom *et al.*, 2009). Lipid peroxidation can be inhibited by antioxidants such as vitamin C and vitamin E, which protect lipids from oxidation (Frank and Gupta, 2005, Mahadik *et al.*, 2001). Notably, levels of malondialdehyde (MDA), which is a byproduct of polyunsaturated lipid degradation by ROS, were found to be significantly increased in depressed patients (Bilici *et al.*, 2001, Khanzode *et al.*, 2003a, Sarandol *et al.*, 2007). Furthermore, studies have demonstrated that lower serum cholesterol and DHA levels are associated with suicide attempts (Brunner *et al.*, 2001, Brunner *et al.*, 2002).

The fatty acid composition of the human brain is the key to maintaining the structural and functional integrity of cellular membrane structures. Recent studies have demonstrated that one of the most important functions of cholesterol and DHA is to form lipid rafts—special, highly-ordered regions on the plasma membrane that are rich in cholesterol, DHA, and sphingolipids (Ferrer, 2009, Pani and Singh, 2009). Lipid rafts function to cluster receptors and proteins involved in signal transduction (e.g. G-protein subunits, adenylyl cyclase), aid in protein scaffolding, and facilitate internalization of G-protein coupled receptors (Ferrer, 2009, Pani and Singh, 2009). A subset of lipid rafts containing caveolin proteins (known as Caveolae) play an important role in modulating synaptic plasticity and neurite outgrowth (Ferrer, 2009, Pani and Singh, 2009). As a major component of lipid rafts, DHA regulates dopaminergic and serotoninergic neurotransmission (Kodas *et al.*, 2002, Zimmer *et al.*, 2000) and signal transduction (Vaidyanathan *et al.*, 1994), and interacts with membrane-bound enzymes (Bourre *et al.*, 1989) and ionic channels (Vreugdenhil *et al.*, 1996). Caveolae are widely expressed in the CNS in brain microvessels, endothelial cells, astrocytes, oligodendrocytes, Schwann cells, dorsal root ganglia, and hippocampal neurons (Allen *et al.*, 2007).

Investigators have suggested that neurotransmitter signaling may occur via clustering of receptors in lipid rafts or caveolae, and the effects of lipid rafts on neurotransmitter signaling

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have been implicated in neurological and psychiatric diseases in general (Nomura *et al.*, 2008, Pani and Singh, 2009), and in mood disorders in particular (Brambilla *et al.*, 2003, Shiah and Yatham, 2000, Donati *et al.*, 2008). Traditionally, the brain systems receiving the greatest attention in neurobiological studies of mood disorders were the monoaminergic neurotransmitter systems (e.g., the serotonergic, dopaminergic, and norepinephrinergic systems) that are extensively distributed throughout the network of limbic, striatal, hippocampal, and prefrontal cortical neuronal circuits (Drevets, 2000, Manji and Duman, 2001, Nestler *et al.*, 2002). However, recent studies show that glutamatergic synaptic plasticity may be the convergence point for the treatment of mood disorders, and alterations in this system are known to play a major role in cellular plasticity and resilience (Sanacora *et al.*, 2008). Existing antidepressants and mood stabilizers have prominent effects on the glutamatergic system, and modulating glutamatergic, ionotropic, or metabotropic receptors results in antidepressant-like properties in animal models (Sanacora *et al*., 2008). The structurally dissimilar mood stabilizing agents lithium and valproate were both found to reduce synaptic expression of the α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) glutamate receptor at synapses in vivo and in vitro in the hippocampus (Du *et al.*, 2008, Du *et al.*, 2003, Du *et al.*, 2004). In contrast, antidepressant agents such as imipramine, lamotrigine, and riluzole enhanced surface AMPA receptor expression and phosphorylation of GluR1S845 in the hippocampus *in vivo* (Du *et al.*, 2007). As a result, several glutamatergic modulators targeting various glutamate components are currently being studied in the treatment of mood disorders, including release inhibitors of glutamate, N-methyl-D-aspartate (NMDA) antagonists, AMPA throughput enhancers, and glutamate

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transporter enhancers (Sanacora *et al.*, 2008). Preliminary pharmacogenetic studies have also strongly implicated glutamatergic signaling in suicidal behaviors (Lekman *et al.*, 2008).

Taken together, these findings suggest that chronic stress damages mitochondrial function and subsequently changes the lipid composition in the brain. The altered lipid composition may have a large impact on the structural and functional integrity of the cellular membrane structure, ultimately leading to aberrant neurotransmitter signaling. This altered neurotransmitter signaling may in turn contribute to the pathophysiology of depression and suicidal behavior (Figure 1).

CURRENT HYPOTHESES REGARDING THE ETIOLOGY OF DEPRESSION AND SUICIDAL BEHAVIORS

Many hypotheses for the pathophysiology of depression and suicidal behaviors have been proposed, and it is beyond the scope of this article to review them all. However, it is interesting to note the large and varied literature on depression implicates (but is not limited to) many different etiologies to varying degrees, including dysfunction or alterations in monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) (Bourin *et al.*, 2002, Owens, 2004, Syvalahti, 1987), oxidative stress (Maes *et al.,2011*), glutamatergic synaptic strength (Du *et al.*, 2004, Du *et al.*, 2007, Zarate and Manji, 2008), mitochondria (Rezin *et al.*, 2008), cytokines (Maes *et al.*, 2009b), homocysteine (Folstein *et al.*, 2007), lipids (including cholesterol and PUFAs) (Su, 2009), neurotrophins or growth factors (Dwivedi, 2009, Molendijk *et al.,2011*), magnesium (Eby and Eby, 2010), zinc (Irmisch *et al.*, 2010), cyclic AMP (cAMP) response element binding (CREB) (Czeh and Simon, 2005), and histone deacetylase (HDAC) (Covington *et al.*, 2009). Finally, stress (Bao *et al.*, 2008), sleep (Fang *et al.,2010*), altered neurotransmitter serotonin signaling (Brown and Gershon, 1993, Nordstrom and Asberg, 1992), lipids (Brunner *et*

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al., 2002, Colin *et al.*, 2003), and neurotrophins (Dwivedi, 2009) have all been proposed as key to the pathophysiology of suicidal behavior.

As regards the hypotheses presented in this paper, several common threads from this disparate literature emerge. For instance, accumulating evidence suggests that chronic stress and sleep deprivation increase cortisol levels (Wolkowitz *et al.*, 2001), which in turn leads to oxidative stress (Madrigal *et al.*, 2001) and high homocysteine levels (Black and Garbutt, 2002, de Souza *et al.*, 2006) and, subsequently, to mitochondrial damage (Madrigal *et al.*, 2001) and lipid degradation (Arts *et al.*, 2007) in neuronal circuits. The lipid raft region is composed of cholesterol, polyunsaturated fatty acids (including EPA, DHA), and sphingolipids and mediates neurotransmitter signaling through G-protein coupled receptors and ion channels (Pani and Singh, 2009). It has been shown that depletion of cholesterol, or EPA and DHA caused a decrease in numbers of lipid raft on the neuronal membrane, which may lead to the aberrant G-protein coupled receptor signaling (Siddiqui *et al*., 2007). It is note-worthy that lower serum cholesterol and DHA levels are associated with suicide attempts (Brunner *et al*., 2001, Brunner *et al*., 2002, Neaton *et al*., 1992). Drugs, which lower the cholesterol levels, are able to cause the depressive symptoms (Tatley and Savage, 2007). In addition, fish-intake (rich in EPA or DHA) directly protects against the onset of major depressive disorder (Weidner et.al., 1992). Moreover, chronic stress induced an inhibition to the respiratory chain in the mitochondria in the brain (Madrigal *et al.*, 2001). Mitochondrial dysfunction caused by changes in biochemical cascade or the damage to the mitochondrial electron transport chain has been suggested to be an important pathogenic factor for the psychiatric disorders, particularly in bipolar disorders and depression (Rezin *et al.*, 2009). Moreover, food supplements, such as B12 or folate, which protects mitochondrial functions are effective as an adjunctive therapy for the treatment of depression（Papakostas *et al*., 2005）. All these studies imply that mitochondrial dysfunction and reduced formation of lipid raft may be involved in the etiology of depression and suicidal behavior (Figure 1). These stress-induced neuronal dysfunctions interact with the other genetic and environmental factors, including adverse childhood events, exposure to trauma, drug abuse, smoking, alcohol usage, sleep, diet, and exercise levels, to precipitate mood disorders in genetically and/or physiologically vulnerable or predisposed individuals (Figure 1). The evidence reviewed here thus provides multiple targets for the treatment of mood and anxiety disorders. Below, we review evidence supporting the ability of several nutrients that are safe and widely-available over the counter to either prevent the onset of these conditions or augment the effects of currently available therapeutics.

OXIDATIVE STRESS, CHOLESTEROL, AND ω3 FATTY ACIDS IN THE PATHOPHYSIOLOGY AND TREATMENT OF DEPRESSION AND SUICIDAL BEHAVIORS

Depression and suicidal ideation are both accompanied by decreased antioxidant levels

Antioxidants are compounds that can quench free radicals by accepting an unpaired electron. In addition to the endogenous antioxidant enzyme systems, food contains many antioxidants, including vitamin E, vitamin C, beta-carotene, leutin, α-lipoic acid, coenzyme Q10 (Co-Q10), lycopene, zeaxanthines, and selenium. Although results from large randomized trials of dietary interventions have yielded mixed results, a number of observational studies have revealed that antioxidants enhance CNS cognition and resilience, particularly in neurodegenerative and psychiatric disorders (Smith and Blumenthal,2010). For instance, accumulating evidence has shown that MDD is associated with decreased antioxidant levels and with the induction of oxidative pathways (Ng *et al.*, 2008, Sarandol *et al.*, 2007). Other studies have noted that individuals with MDD have significantly lower plasma concentrations of a number of key antioxidants, including vitamin C, vitamin E, zinc, and Co-Q10 (Khanzode *et al.*, 2003b, Maes *et al.*, 2009a). One study suggested that lowered blood concentrations of zinc, CoQ10, vitamin E, vitamin C, and GSH might contribute to a lowered total antioxidant capacity (TAC), which was noted to be significantly lower in 57 patients with MDD than in 40 healthy volunteers (Cumurcu *et al.*, 2009). A significant and inverse correlation was also noted between TAC and severity of depression using the Montgomery-Asberg Depression Rating Scale (MADRS) (Galecki *et al.*, 2009). Lower antioxidant enzyme activity (e.g. glutathione peroxidase (GPX)), is another feature of depression(Ozcan *et al.*, 2004) . It is interesting to note that MDA levels were found to be significantly higher in depressed patients, and may therefore serve as a biomarker for depression (Chang *et al.*, 2009). Long-term stress also causes oxidative damage to DNA (Irie *et al.*, 2005). One of the oxidative stress modifiers of DNA is 8—dehydroxyguanisine (8-OH-dG); levels of this compound were positively associated with depressive symptoms (Irie *et al.*, 2003).

Although the evidence to date is preliminary, levels of antioxidants, vitamins, and carotenoids have also been found to be lower in patients with a history of suicide attempts (Li *et al.*, 2007). Investigators have speculated that lowered antioxidant capacity may impair protection against ROS, thus damaging fatty acids (Edwards *et al.*, 1998, Maes *et al.*, 1999). As noted above, PUFAs are particularly vulnerable to lipid peroxidation.

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Lower ω3 fatty acid and serum cholesterol levels are associated with suicide attempts and MDD

Epidemiological studies have identified low fish (high in ω-3 fatty acid) consumption as a risk factor for mortality from suicide (Hibbeln and Salem, 1995, Hirayama, 1990, Sublette *et al.*, 2006, Tanskanen *et al.*, 2001). One study noted that frequent fish consumption (twice per week or more) significantly reduced the risk of depressive symptoms and of self-reported suicidal ideation (Tanskanen *et al.*, 2001). A 17-year follow-up study of over 250,000 Japanese subjects showed that people who ate fish daily had a lower risk of death from suicide (Hirayama 1990). In addition, several reports indicate that lower ω3-fatty-acid levels, including lower plasma EPA, and DHA, or EPA in red blood cells, predicted greater risk of suicide attempt (Hibbeln and Salem, 1995, Huan *et al.*, 2004, Sublette *et al.*, 2006). Because both cholesterol and DHA are major components of the lipid raft, it is possible that reduced cholesterol and ω3-fatty-acid levels may affect the formation of lipid rafts in the CNS, and subsequently reduce neurotransmitter signaling (Czysz and Rasenick, 2013). Notably, increased formation of lipid rafts in the membrane would facilitate serotonergic (Donati *et al.*, 2008, Renner *et al.*, 2007), dopaminergic (Villar *et al*., 2009), and glutamatergic (Francesconi *et al.*, 2009, Ponce *et al.*, 2008) neurotransmitter signaling; all of these play important roles in the pathophysiology and treatment of psychiatric disorders. Studies have noted that low cholesterol levels are associated with increased risk of suicide (Neaton *et al.*, 1992) and that this association shows an inverse relationship with baseline total serum cholesterol (Lester, 2002, Lindberg *et al.*, 1992). Other studies found that individuals who attempted suicide had significantly lower cholesterol levels than controls (Atmaca *et al.*, 2002, Boston *et al.*, 1996, Kim *et al.*, 2002, Kunugi *et al.*, 1997,

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Maes *et al.*, 1997a, Modai *et al.*, 1994, Rabe-Jablonska and Poprawska, 2000, Sarchiapone *et al.*, 2001, Takei *et al.*, 1994). A postmortem study found that the brains of violent suicide completers had a lower grey-matter cholesterol content (Lalovic *et al.*, 2007), and that a family history of suicidal behavior was more frequent among carriers of Smith–Lemli–Opitz syndrome, an autosomal recessive disorder characterized by abnormally low cholesterol levels (Lalovic *et al.*, 2004).

Similarly, many studies have reported an association between low cholesterol levels and depression (Cadeddu *et al.*, 1995, Lindberg *et al.*, 1994, Maes *et al.*, 1994, Morgan *et al.*, 1993, Olusi and Fido, 1996, Suarez, 1999), including a large Finnish study involving over 29,000 men (Partonen *et al.*, 1999). Low cholesterol levels have been found to confer increased risk of MDD (Partonen *et al.*, 1999), and to correlate with severity of depressive symptoms in samples of elderly men (Morgan *et al.*, 1993), middle-aged women (Horsten *et al.*, 1997), and depressed patients (Rabe-Jablonska and Poprawska, 2000, Rafter, 2001, Steegmans *et al.*, 2000). Studying cholesterol in depression may also help identify factors that place these patients at risk for non-response to treatment (Sonawalla 2002). Relatedly, use of cholesterol synthesis inhibitor statins (functionally HMG-CoA reductase inhibitors), which lower serum cholesterol levels, has been associated with psychiatrically adverse reactions, particularly depression and memory loss (Tatley and Savage, 2007).

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The role of antioxidants and members of the vitamin B family in enhancing cognition and resilience, and in the treatment of mood disorders

Human studies as well as animal models of depression provide evidence suggesting that oxidative damage is involved in treatment resistance and in the working mechanisms of antidepressant agents (Alpert *et al.*, 2002, Papakostas *et al.*, 2004). For instance, one recent clinical study found that N-acetyl-cysteine (NAC), a potent antioxidant that up-regulates the glutathione pathway, significantly augmented the clinical efficacy of antidepressants and mood stabilizers in individuals with bipolar disorder (Berk *et al.*, 2008).

Vitamin C (ascorbate) is a water-soluble vitamin that can be oxidized (dehydroascorbate). Dehydroascorbate can be recycled to ascorbate through endogenous antioxidant enzymes and glutathione. Several studies found that taking a combination of vitamin C and vitamin E supplements enhanced cognitive function in the elderly (Morris *et al.*, 2002, Pettenuzzo *et al.*, 2002). Vitamin C was also associated with antidepressant effects in patients with depression, secondary to adrenocorticotropic hormone (ACTH) treatment (Cocchi *et al.*, 1980). It was effective as an adjunctive treatment to fluoxetine (Amr *et al*., 2013), and improved mood—as assessed by the penile-vaginal intercourse (FSI),—in healthy young adults (Brody, 2002).

Another key vitamin is folic acid, which cooperates with vitamin B12 to promote the regeneration of methionine from homocysteine. Homocysteine is toxic to mitochondrial function (Coppen and Bolander-Gouaille, 2005, Paul *et al.*, 2004) and, as noted previously, higher homocysteine levels have been associated with depression. In addition, methionine can be converted to S-adenosylmethionine (SAMe), which is the principal methyl donor in the brain. Double-blind, clinical trials demonstrated that, when used adjunctively with standard selective serotonin reuptake inhibitors (SSRIs), SAMe had antidepressant effects in patients with MDD (Papakostas, 2009). Studies have linked lower folic acid levels to depression in elderly women (Ramos et al 2004), in a middle-aged community sample (Sachdev *et al.*, 2005), and in male smokers (Sanchez-Villegas 2009). Vitamin B12 was similarly linked to depressive symptoms in women (Sanchez-Villegas 2009). In addition, folate depletion has been linked to disturbed metabolism of serotonergic and other biogenic amines. In studies of individuals with MDD treated with fluoxetine, low folate levels were associated with delayed onset of clinical improvement (Papakostas *et al.*, 2005), as well as treatment resistance (Papakostas *et al.*, 2004). Moreover, co-administration of methylfolate, a highly absorbable form of folic acid, has been found to augment the effects of SSRIs (Coppen and Bailey, 2000, Godfrey *et al.*, 1990, Roberts *et al.*, 2007)

Zinc is another mineral with antioxidant properties (Powell, 2000), and accumulating data suggest a relationship between low serum zinc levels and severity of depression (Maes *et al.*, 1997b, Siwek *et al.*,2010). Zinc deficiency increases ROS, which could harm mitochondrial function (Corniola *et al.*, 2008). Notably, various animal studies have demonstrated that zinc has antidepressant effects either alone or as an augmentation strategy for traditional antidepressants (Nowak *et al.*, 2003, Sowa-Kucma *et al.*, 2008). These effects are hypothesized to be related to zinc's anti-oxidative properties, effects on PUFA metabolism, and neurogenesis stimulation through increased gene expression of brain-derived neurotrophic factor (BDNF) (Maes *et al.*, 1997b, Siwek *et al.*,2010). A recent double-blind, placebo-controlled study of daily zinc supplementation to imipramine therapy in patients with MDD found that MADRS scores were significantly negatively correlated with serum zinc levels; furthermore, treatment-resistant patients with MDD had lower zinc concentrations than patients who were not treatment-resistant (Siwek *et al.*,2010).

Finally, magnesium is key to numerous enzymatic reactions involving the formation and use of ATP in energy metabolism. In addition, it is also a NMDA receptor blocker that controls calcium entry to the neurons (Eby and Eby, 2010). It is noteworthy that, in both animal studies and individuals with treatment-resistant MDD, the NMDA antagonist ketamine has rapid and long-lasting anti-depressant effects (Zarate *et al.*, 2006). Case studies have noted that both iv (Enya *et al.*, 2004) and oral magnesium were associated with rapid resolution of depressive symptoms secondary to various disorders, including MDD (Eby and Eby, 2006). In addition, in a double-blind randomized clinical trial, it was shown that magnesium was as effective as imipramine in treating depressive symptoms in elderly patients with Type II diabetes (Barragan-Rodriguez *et al.*, 2008).

ω3 fatty acids in enhancing cognition and resilience, and treating mood disorders

One study found that increased fish intake, even combined with a cholesterol-lowering diet, decreased depressive symptoms (Weidner *et al.*, 1992). Diverse studies—including epidemiological studies, case-control comparisons of blood and brain tissues, double-blind, randomized, placebo-controlled trials, and meta-analyses of these trials—have consistently indicated that low fish (high in ω-3 fatty acid) consumption or low ω3 body compositional status increases the risk of depression and other affective illnesses (Sinclair *et al.*, 2007).

Both preclinical and clinical studies have shown that PUFA uptake enhances cognitive function (Richardson *et al.*, 2003). Both local synthesis and uptake are thought to contribute to

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the brain pool of DHA; in animal studies, a DHA- and cholesterol enriched diet improved spatial learning in the Morris water-maze paradigm (Hooijmans *et al.*, 2009). In humans, a double-blind, randomized, placebo-controlled study with one-way crossover (placebo to active treatment) reported improvements in reading, spelling, and behavior in children with developmental coordination disorder who received EPA, DHA, and γ-linolenic acid supplements (Richardson *et al.*, 2003).

The role of ω3 fatty acids in the treatment of depression has been extensive (see Table 1 for a summary). A recent meta-analysis of ω3 fatty acid treatment trials in depression that included data from more than twelve independent studies (Table 1) showed that consistent therapeutic benefits were associated with adjunctive use of the ω3 fatty acid EPA over placebo (Martins, 2009). Indeed, most of the clinical trials using predominantly 1-2g EPA/day exhibited significant beneficial effects in depression patients (Hallahan *et al.*, 2007, Jazayeri *et al.*, 2008, Mischoulon *et al.*, 2009, Nemets *et al.*, 2002, Peet and Horrobin, 2002, Su *et al.*, 2003, Su *et al.*, 2008a). However, several clinical trials using DHA or fish oil enriched with DHA showed no beneficial effect for treating MDD or perinatal depression (Freeman *et al.*, 2008, Grenyer *et al.*, 2007, Marangell *et al.*, 2003, Rees *et al.*, 2008, Silvers *et al.*, 2005). The effectiveness of ω3 fatty acids has also been evaluated in the treatment of bipolar depression, where two of three placebo-controlled, double-blind trials found a beneficial effect over placebo (Clayton *et al.*, 2009, Stoll *et al.*, 1999). This effect may be related to the regulation of intracellular phospholipase A2 activity (Smesny et al., 2013). In addition, ω3 fatty acid treatment was also beneficial in the treatment of schizophrenia (Nakagome *et al.*, 2009, Peet, 2003).

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Studies have also evaluated the utility of ω3 fatty acids for preventing suicidal behaviors. In a randomized, double-blind, placebo-controlled trial of patients recruited from an emergency room who had exhibited recurrent self-harm behaviors, 2g/day of ω3 long chain fatty acids led to a 45% reduction in suicidal thinking, and a 30% reduction in depressive symptoms (Hallahan *et al.*, 2007).

CONCLUDING REMARKS

This manuscript has summarized the existing evidence that ω3 fatty acids, antioxidants, B family vitamins, zinc and magnesium protect mitochondrial function and enhance neurotransmitter signaling in the brain. In addition, reduced ω3 fatty acids, oxidative capacity, B-12, and folic acid levels have been associated with both depression and suicidal ideation in humans. The question is the extent to which administration of these particular nutrients may exert beneficial effects on depressive symptoms or suicidal ideation. We have listed the components and side effects for the nutrients in Table 2.

While this is an issue of considerable importance for public health, it has particular urgency in military populations. Numerous recent studies have called for a way to address prevention and more effective treatment strategies for depression and suicidal ideation in both civilian and military populations. There appears to be a strong relationship between duration of combat exposure and the severity of mental illness (Dohrenwend, 2006), suggesting that the severity of stress may play a role. Specifically, repeated exposure to combat and multiple deployments might work as a repetitive severe stressor in this situation, in addition to being an "anticipatory stressor" (e.g, worrying about what will happen) as well as associated with physiological

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stressors (e.g., sleep deprivation) (Selby *et al.,2010*). Indeed, cumulative studies have shown that exposure to combat is a risk factor for both PTSD (Lapierre, 2008) and depression (Lapierre *et al.*, 2007) in soldiers. Not surprisingly, injured soldiers also report more depressive and suicidal problems (McAllister, 2009). Furthermore, PTSD is strongly linked to suicidal behavior (Kessler, 2000). As reviewed above, psychological repetitive stress, traumatic experience, and sleep deprivation were all shown to cause oxidative stress and mitochondrial damage in the brain (Du *et al.*, 2009, Jou *et al.*, 2009, Su *et al.*, 2008b, Zhang *et al.*, 2006). Most of the civilian clinical trials cited in this paper cover a wide age range including that of most soldiers.

The multiple nutrients reviewed here affect stress-related damage to mitochondrial function and neurotransmitter signaling at different levels in order to power a therapeutic benefit. Specifically, 1) the antioxidants vitamin C would increase oxidative status during stress, and zinc would enhance the antioxidant effect; 2) vitamin B12 and folic acid would reduce the level of the toxic homocysteine and enhance the formation of antidepressant SAMe; 3) the essential ω3 fatty acids would support the function of lipid rafts; and 4) magnesium would facilitate mitochondrial enzyme function and block the calcium entry from NMDA receptors (Figure 2). As noted above, previous studies have shown that antidepressant drug resistance is associated with low serum levels of folic acid (Papakostas *et al.*, 2004), vitamin B12 (Papakostas *et al.*, 2004), magnesium (Eby and Eby, 2010) and antioxidant status (Maes *et al.*, 2009a). Thus, these nutrients could be of considerable utility in either preventing the onset of mood disorders and suicidal behaviors in vulnerable individuals, or significantly augmenting the therapeutic effect of available drugs. Furthermore, because these nutrients are well known to be safe and reliable, implementing their use could be an easy way to protect individuals against stress-related psychiatric disorders, including PTSD, depression, and suicide attempts. Controlled clinical trials, both preventive and therapeutic, in both civilian and military populations, are warranted.

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DISCLOSURE/CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose, financial or otherwise.

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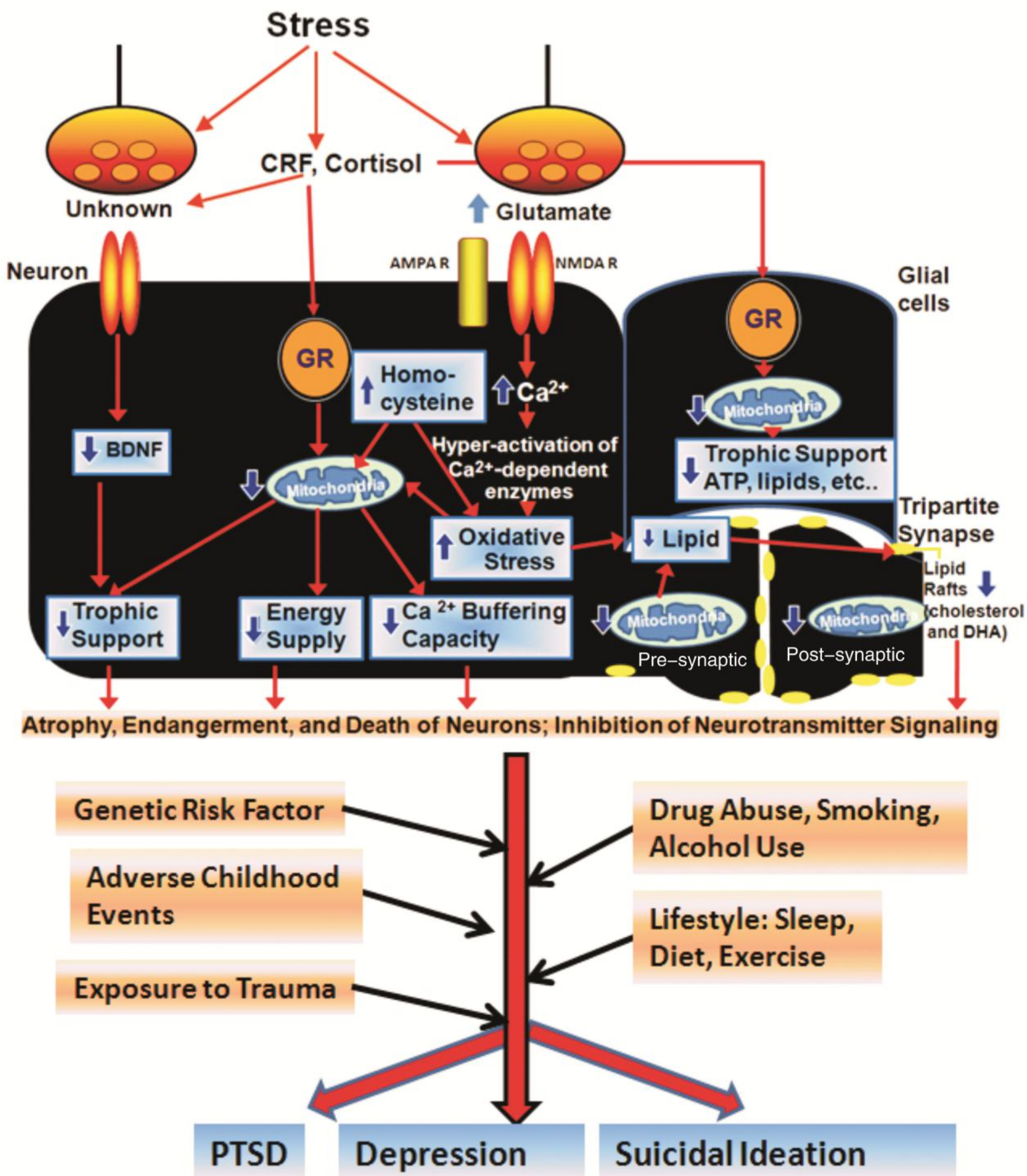

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Figure 1. Stress-induced damage to mitochondrial function and neurotransmitter signaling in the pathophysiology of PTSD, depression, and suicidal ideation.

Chronic stress and sleep deprivation increase cortisol (which binds to its receptor, glucocorticoid receptor, GR) and corticotrophin releasing factor (CRF), followed by enhanced oxidative stress and higher homocysteine levels, which subsequently lead to mitochondrial dysfunction and lipid degradation in the neurons in the circuits mediating cognitive, affective, motoric, and neurovegetative functions. In addition, it was reported that chronic stress lead to down-regulation of neurotrophic factor brain-derived neurotrophic factor (BDNF) expression, which may also contribute to the chronic stress-induced neuronal damage. Chronic stress also increases intracellular glutamate levels, which may cause altered calcium signaling and oxidative stress in the neurons. Glial cells include the astrocytes, oligodendrocytes, and microglia. Tripartite synapse represents the pre-synaptic structure, the post-synaptic structure and the surrounding astrocyte as a functional unit. Astrocytes sense and regulate synaptic activity depending on intracellular Ca^{2+} levels. Mitochondria provide trophic support, energy, and calcium-buffering capacity in the neuronal cell body, the astrocytes, the dendrites, and the synapses. Mitochondrial dysfunction and altered lipid rafts may lead to aberrant neurotransmitter signaling, dendritic atrophy, and neuronal endangerment. This stress-induced neuronal damage interacts with genetic and environmental factors, including adverse childhood events, exposure to trauma, drug abuse, smoking, alcohol use, sleep, diet, and exercise levels to eventually precipitate mental illness in vulnerable individuals. Depending on the severity of these factors, and an individual's personal

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predisposition, the course of the illness may develop towards a variety of psychiatric disorders.

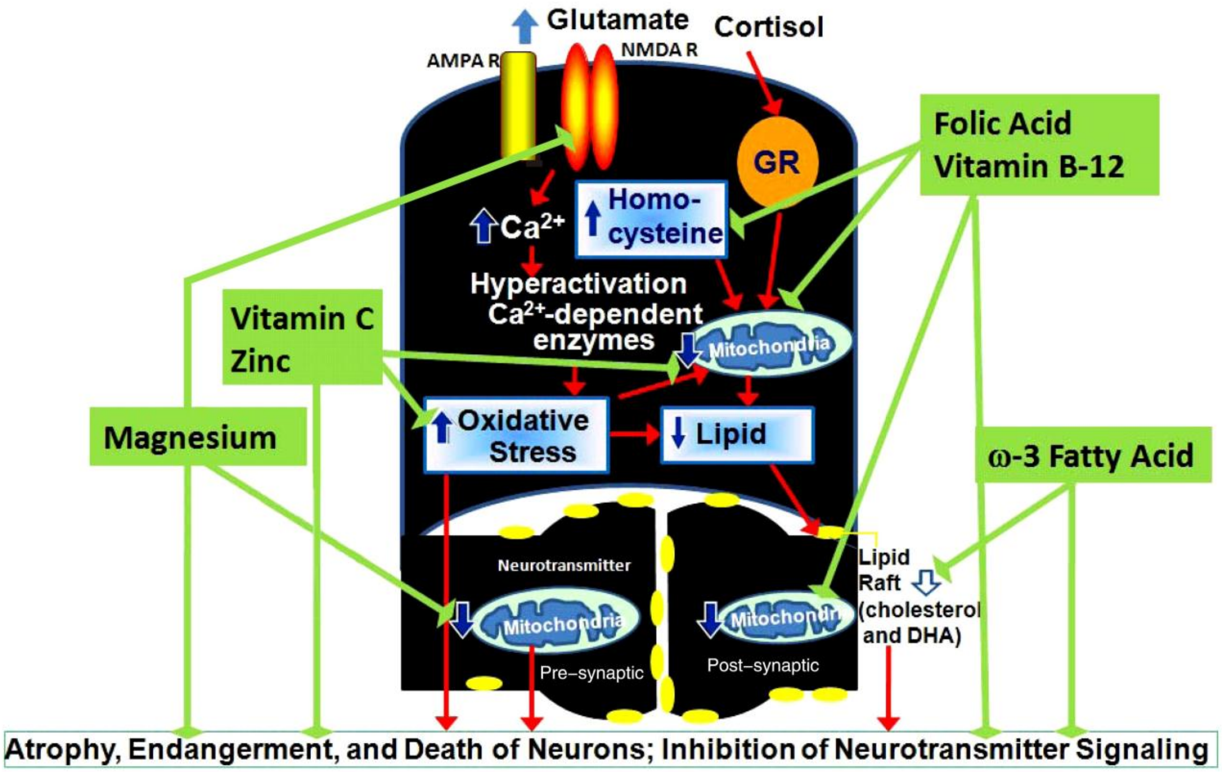

Figure 2. Nutrients protect mitochondrial function and neurotransmitter signaling against stress-induced neuronal damage.

Chronic stress causes increases of the cortisol level and the intracellular glutamate level in the brain. The high levels of cortisol may cause increased oxidative stress and higher homocy steine levels, which subsequently lead to mitochondrial dysfunction and lipid degradation. The in tra-cellular glutamate activates the N-methyl-D-aspartic acid receptor (NMDA R) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPA R) and induces calcium influx, which leads to hyperactivation of the Ca^{2+}dependent enzymes and oxidative stress. The higher level of lipid oxidation may result in lipid degradation and lower levels of Eicosapntemacnioc Acid (EPA), Docosahexaenoic Acid (DHA), or other polyunsaturated fatty acid (PUFA) in the brain for the formation of the lipid rafts, followed by a decrease in the number of lipid rafts, which may affect the G-protein coupled receptor signaling at the synapses. ω3 fatty acids, vitamin C, folic acid, vitamin B12, zinc, and magnesium protect mitochondrial function and neurotransmitter signaling. In particular, ω3 fatty acids facilitate the formation of lipid rafts, which mediate neurotransmitter signaling. Vitamin C and zinc balance stress-induced oxidative stress during chronic stress situations. Vitamin B12 and folic acid reduce homocysteine levels, and enhance the formation of S-adenosylmethionine (SAMe). Magnesium is a co-enzyme for energy production in the mitochondria. It is also an NMDA antagonist that blocks excessive calcium influx and protects neurons.

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Table 1. Clinical studies exploring the use of nutrients in treating depression and suicidal behaviors.

	Clinical trial	Design	Participants	Interventions	Outcomes	Conclusion
ω3	Haberka et.al. 2013[a]	Randomized, standard therapy control.	52 patients with acute myocardial infarction.	n-3 PUFA 1g/day + standard therapy.	BDI STAI-S STAI-T ESQ	Significantly reduced depressive and anxiety symptoms
	Mozurkewich et.al. 2013[b]	Double blind, randomized, controlled.	126 pregnant women at risk for depression.	EPA-rich fish oil (1060 mg EPA plus 274 mg DHA), DHA-rich fish oil (900 mg DHA plus 180 mg EPA)	BDI	No significant difference.
	Krawczyk et.al. 2013[c]	Control group, antidepressant treatment with lithium and lamotrigine.	21 patients diagnosed with a treatment-resistant depression.	2.2g of EPA, 700mg of DHA, 240mg of GLA, 40mg of vitamin E, primrose oil.	HDRS scale	Marked improvement in depressive symptom.

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	Gertsik et.al. 2012[d]	Randomized, masked, placebo-controlled.	42 patients diagnosed with major depression.	Two 1g capsules containing a bend of 900mg of EPA, 200mg of DHA and 100mg of other omega-3 fatty acid, twice daily plus citalopram.	HDRS	Combination therapy was more effective and demonstrated significant better HDRS score.
	Mischoulon et.al. 2009[e]	Double blind, randomized, placebo-controlled.	35 patients with DSM-IV diagnosed major depression. Mean age: 45.	EPA 1g/day (16), or placebo (19) for 8 weeks	HDRS	EPA was superior to placebo, but the effect did not reach statistical significance because of small sample size (p=0.087).
	Jazayeri et.al. 2008[f]	Double blind, randomized, placebo-controlled.	60 patients with DSM-IV diagnosed major depression. Age range: 20-59.	Fluoxetine 20mg/day (16), EPA 1g/day (16), or fluoxetine plus EPA (16) for 8 weeks.	HDRS	EPA 1g/day was as effective as fluoxetine. EPA plus fluoxetine was superior to either agent alone.
	Rees 2008[g]	Double blind, randomized, placebo-	26 patients with DSM-IV diagnosed perinatal depression. Mean age:	Fish oil, 6g/day (0.4g EPA/day, 1.64g DHA /day) (13), or	EPDS, HDRS	Fish oil (0.4g EPA/day; 2.2gDHA/day) showed no significant effect as monotherapy

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		controlled.	33.	placebo (13) for 6 weeks.		for perinatal depression.
	Su 2008[h]	Double-blind, randomized, placebo-controlled.	36 pregnant women with DSM-IV diagnosed major depression. Mean age: 31	2.2g EPA/day plus 1.2g DHA/day (18), or placebo (18) for 8 weeks.	BDI, EPDS, HDRS-21	The group receiving EPA and DHA as monotherapy had significantly lower depression rating scale scores than those receiving placebo
	Freeman 2008[i]	Randomized, placebo-controlled.	59 patients with DSM-IV diagnosed perinatal depression. Mean age: 30	1.9g EPA and 1.9g DHA/day (28), or placebo (31) for 6 weeks.	EPDS HDRS, CGI	No significant difference between the EPA/DHA and placebo groups
	Mischoulon 2008[j]	Double-blind, randomized, placebo-controlled.	35 patients with DSM-IV diagnosed major depression. Mean age: 42.	DHA 1g/day (14), DHA 2g/day (11), DHA 4g/day (10), for 12 weeks	HDRS	Patients receiving either 1g or 2g per day of DHA had significant increases in their HDRS scores.
	Hallahan 2007[k]	Randomized,pla-cebo- controlled.	49 patients with history of repeated self-harm. Mean age:	EPAX 5500 (1.2g EPA/ day, 0.9 DHA/day) (22) or placebo (27) for 12	HDRS, BDI	EPA/DHA treatment substantially reduced surrogate markers for suicidal behavior and depression

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			30.	weeks.		score.
	Grenyer 2007[l]	Double-blind, placebo-controlled.	83 patients with major depression, age range 18-65.	Regular antidepressants, plus 0.6g EPA/day or 2.2g DHA/day, for 16 weeks.	HDRS, BDI	Tuna fish oil (0.6g EPA/day, 2.2g DHA/day) had no significant beneficial effects.
	Silvers 2005[m]	Double-blind, placebo-controlled.	77 patients with clinically diagnosed major depression . Mean age: 39.	Standard antidepressants plus 8g tuna fish oil (0.6g EPA, 2.4g DHA) (40), or placebo (37) for 12 weeks.	HDRS, BDI	Mood improved significantly for all patients, including those receiving placebo. Fish oil did not improve mood more than placebo.
	Marangell 2003[n]	Double-blind, placebo-controlled.	36 patients with DSM-IV diagnosed major depression, age range 18-65.	Standard antidepressant plus DHA 2g/day (18), or placebo (17) for 6 weeks.	HDRS, MADRS	DHA 2 g/day showed no significant benefit.
	Su 2003[o]	Double-blind, placebo-controlled.	28 patients with DSM-IV diagnosed major depression. Mean age:	Antidepressants plus 9.6g ω3 fatty acid (4.4g EPA, 2.2g DHA) (11) or	HDRS-21	Significantly lower HDRS score in the group receiving ω-3 fatty acids.

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			37	placebo (17) for 8 weeks.		
	Nemets 2002[p]	Double-blind, randomized, placebo-controlled,	20 patients with DSM-IV diagnosed major depression. Age range: 28-73.	Standard antidepressant plus 2g EPA/day (10), or placebo (10) for 3 weeks	HDRS	Highly significant benefits for EPA compared to placebo.
	Peet and Horrobin 2002[q]	Double-blind, randomized, placebo-controlled, stratified by sex.	70 depressed patients with a HDRS score >15. Mean age: 44.	Standard antidepressant plus 1g EPA/day (14), 2g EPA/day (18), 4g EPA/day (17), or placebo (19) for 12 weeks.	HDRS, MADRS, BDI	Highly significant improvement with 1g EPA/day treatment. No effect for 2gEPA/day or 4g EPA/day.
Vitamin C	Amr et.al.2013[r]	Radomized, double-blind, placebo-controlled.	24 pediatric patients with depression.	Fluoxetine(10-20mg/day) plus vitamin C（1000mg/day）or placebo.	CDRS, CDI, CGI.	Vitamin C may be an effective adjuvant agent in the treatment of MDD in the pediatric patients.
	Brody 2002[s]	Double-blind, randomized, placebo-	81 healthy subjects, mean age 24.4.	Vitamin C 3000mg/day (42), or placebo (39) for 2 weeks.	BDI	Vitamin C significantly reduced the BDI scores.

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		controlled.				
	Cocchi 1980[t]	Case series, depression secondary to ACTH treatment of pediatric hepatitis.	4 cases of "idiopathic" depression (ages 5, 7, 19, and 29).	Vitamin C 50mg/kg/day, for 2 weeks	Symptom-based diagnosis	Completely recovery from psychiatric disturbance.
Folate, B12, .	Almeida 2010[u]	Double-blind, randomized, placebo-controlled.	273 stroke survivors, Mean age:63.	Folic acid (2mg/day), vitamin B6 (25mg/day), vitamin B12 (0.5mg/day) (136), and placebo (137) for 1-10.5 years.	MINI (2006)	B-vitamins were associated with a lower hazard of depression compared to placebo.
	Resler 2008[v]	Double-blind, randomized, placebo-controlled.	27 patients with DSM-IV diagnosed major depression age range: 26-49.	Fluoxetine (20mg/day) plus folic acid (10mg/day) (14), or placebo (13), for 6 weeks.	HDRS	Folic acid significantly lowered the HDRS score as an adjunctive therapy.

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	Coppen 2000[w]	Double-blind, randomized, placebo-controlled, stratified by sex.	127—major depression (DSM III), age mean: 44.	20mg fluoxetine/day plus 500 mcg/day folic acid (51), or 20mg fluoxetine/day plus placebo (58) for 10 weeks.	HDRS	Folic acid greatly improved the antidepressant action of fluoxetine.
	Godfrey 1990[x]	Double-blind, randomized, placebo-controlled, stratified by diagnosis.	24 patients with DSM-III-diagnosed major depression and RBC folate<200ug/l, age range:20-70	Standard antidepressant treatment plus 15 mg methyl-tetrahydrofolate (12), or placebo (12) for 6 months.	HDRS	Clinical and social recovery was significantly improved in those receiving methylfolate plus standard antidepressants compared with those receiving placebo.
	Passeri 1993[y]	Double-blind, randomized, placebo-controlled.	96 patients with DSM-IIIR-diagnosed dementia, MMSE 12-23, HDRS>17 RBC folate 175-700ng/ml, age>65.	Standard antidepressant treatment plus 50 mg methyltetrahydrofolate (47), or trazodone (49) for 8 weeks.	HDRS	Methyltetrahydrofolate was as effective as trazodone in significantly reducing HDRS scores.

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Mg	Barragan-Rodrigues 2008[z]	Randomized clinical trial.	23 elderly patients with depression, type-2 diabetes and hypomagnesemia	50ml MgCl2 5% solution (450mg) or 50mg imipramine for 12 weeks.	Yasavage and Brink Score	Depression scores were identical for the magnesium- and imipramine-treated groups.
	Eby 2006[aa]	Case series.	4 patients with depression, hypomanic depression, or postpartum depression (ages: 23, 35, 40, 59).	Magnesium 125-300mg/day, for 4-7 days.	Symptom-based diagnosis.	Depression was reduced or patients were symptom-free after 4-7 days.
	Enya 2004[bb]	Case report.	1 patient with Gitelman's syndrome-related depression and hypokalemia, age: 69.	Spironolactone (25mg/day) and Magnesium Sulfate (20mEq/day, i.v. injection) for two days	Symptom-based diagnosis	Depressive symptoms disappeared after the second day of i.v. magnesium.
Zn	Siwek	Double-blind, randomized,	60 patients with DSM-IV diagnosed unipolar	Imipramine (~140mg/day) plus 25mg	HADRS, BDI,	Zinc augmented the antidepressant effect of

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	2009[cc]	placebo-controlled,	depression, age range: 18-55.	zinc/day (30), or plus placebo (30) for 12 weeks.	MADRS	imipramine in treatment-resistant patients. No effect on patients who were not treatment-resistant.
	Nowak 2003[dd]	Double-blind, placebo-controlled, stratified by sex.	15 patients with DSM-IV diagnosed major depression, age range: 25-57.	Standard antidepressant plus zinc 25 mg/day (6), or placebo (9) for 6 or 12 weeks.	HDRS, BDI	Zinc supplementation significantly reduced depression rating scale scores after 6 or 12 weeks.

HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; BDI: Beck Depression Inventory; EPDS Edinburgh Postnatal Depression Scale. MINI: Mini-International Psychiatric Interview.

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Table 2. The safety and side effects of the nutrients.

Over-the-counter Nutrient	Effective dose in the clinical trials	Maximum Safe Dose for Long Term Usage*	Side Effects*
ω3 fatty acid	1000mg EPA/day (Jazaveri 2008)	One report says 21g/day	No side effect.
Vitamin C	3000mg/day (Brody 2002)	2000mg/day	No side effect. Large doses of vitamin C can deplete the body's supply of copper. People with kidney stones or kidney failure and people taking ampicillin, indomethacin, alsalate, or tetracycline should consult their doctor.
Folic acid	500mcg/day (Coppen 2000)	400mcg/day	No side effect.
Vitamin B12	500mcg/day (Almaida 2010)	3000mcg/day	Oral Vitamin B12 has no side effects.
Magnesium	150-300mg/	350mg/day	No side effect is associated with this dose.

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	day(Eby 2006)		
Zinc	25mg/day (Siwek 2010)	50mg/day under supervision	High doses of zinc affect the absorption of iron and copper. Zinc should be taken with food to avoid irritating the stomach. People with liver damage or an intestinal disorder should consult their doctor before taking supplementary zinc.

