VIEWPOINT

Depression: Does nutrition have an adjunctive treatment role?

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Abstract
Depression is a serious illness, affecting more than one million Australians each year. It causes significant morbidity and is a major risk factor for deliberate self-harm and suicide. Depression was traditionally viewed as a personality weakness, for which few treatment options were available. The simplistic view that depression is a personality weakness has changed in recent times. Depression is now widely recognised as a mood disorder with underlying biological (biochemical and genetic) and psychosocial causes and as such is responsive to a number of different treatments. The aim of the present paper is to review the literature related to dietary manipulation and how manipulation may assist in treating this illness. Evidence reviewed supports a potential therapeutic benefit of n-3 polyunsaturated fatty acids for the alleviation of negative symptoms associated with depression. Omega-3 polyunsaturated fatty acids, optimal omega balance, folate, tryptophan, vitamin B6, B12, S-adenosyl-L-methionine and Hypericum perforatum may all serve as adjuncts to psychosocial and pharmacological therapies, with positive implications for long-term prognosis.

Key words: clinical nutrition, diet education, diet practice, diet therapy, fatty acid, nutritional research.

INTRODUCTION
The aim of the present paper is to review the literature related to depression and to elucidate how dietary manipulation might help ameliorate the effects of this illness. Clinical depression is a unipolar mood disorder characterised by a pervasive negative mood (persisting for greater than 14 consecutive days) accompanied by a generalised loss of interests, an inability to experience pleasure and suicidal tendencies. It is costly in terms of human suffering and health service use, and has severe implications on physical health.1 Until recently, many Australians had limited knowledge and inaccurate beliefs about mental health problems, and people who suffer from depression were all too often stigmatised and ostracised from society.1 Fortunately, this situation is now gradually changing as government and public health initiatives help to increase community awareness and understanding of depression, with the successful implementation of beyondblue and the Black Dog programme, to name a few.2,3 The causes of depression can be biological, including genetic and biochemical causes, and psychosocial, which involves upbringing, emotional experiences, cultural and environmental influences as well as interpersonal behaviours and interactions.4

Depression is a treatable condition, with early intervention and treatment underpinning an optimistic prognosis. Styron observed, in the account of his own depressive episode, that ‘acute depression inflicts few permanent wounds’.5 The overriding concern in very severe cases is to ensure the safety of the depressed person, both from deliberate self-injury and inappropriate...
risk-taking behaviour. Once stabilised, the main goal of management is to reverse the lowered mood, using a combination of non-pharmacological and pharmacological treatments.4

Psychotherapy includes such techniques as cognitive behaviour therapy and interpersonal therapy, where a person’s negative thoughts, attitudes and beliefs are challenged and positively refocused.6 Medication may prove necessary where psychotherapy alone does not elicit satisfactory results.6 Electroconvulsive therapy, a treatment for severe refractory depression used only after psychotherapy and pharmacotherapy have failed over some time period, may prove necessary in more severe forms of depression.6

The antidepressant drugs fall into three main groups—the tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors and serotonin and noradrenaline reuptake inhibitors (SSRIs, SNRIs).7 Many studies have confirmed that these drugs are effective; however, long-term use gives rise to a number of common and unpleasant side effects, such as weight gain, gastrointestinal disturbances (xerostoma, indigestion, gastric ulceration and constipation), blurred vision, drowsiness and dizziness.7 An additional requirement when taking MAOIs is strict dietary restriction of foods containing high levels of tyramine. The list of tyramine-containing foods is extensive and includes many common foods, such as bananas, avocado, soy products, cheese, coffee and tea.7,8

Although newer antidepressant drugs such as the SSRIs and SNRIs (with fewer side effects in the short to medium term) have been developed to reduce adverse effects, there is still considerable interest in the medical arena to search for safe and effective alternatives.8 This is reflected in the great deal of current research investigating the links between dietary components and the development and treatment of depression. One of the most active areas of research concerns the relationship between the omega-3 long-chain polyunsaturated fatty acids (PUFAs) and depression and the use of omega-3 fatty acid supplements in the treatment of depression.9,10 Other nutrients and ‘natural’ substances identified as having potential implications in the treatment of depression are folate, tryptophan, vitamin B6, B12, S-adenosyl-L-methionine (SAMe) and Hypericum perforatum.11 The aim of the present review is to investigate the adjunctive role of nutrition in the treatment of depression.

PREVALENCE

Depression is one of the most common mental health problems in the general population. The World Health Organization estimates that major depressive disorders will become the second leading cause of disability worldwide by the year 2020, after ischaemic heart disease.11 In the report titled ‘The Global Burden of Disease’, Murray and Lopez comprehensively assessed the mortality and disability from all diseases, injuries and risk factors using inclusive methodological approaches.12 The summary of this landmark study highlighted the finding that ‘the burden of mental illnesses, such as mood disorders, alcohol and drug dependence and schizophrenia have previously been seriously underestimated by approaches that focus on mortality, rather than morbidity and mortality’.12

In Australia, depression is currently the leading cause of non-fatal disability, with analysis of statistics showing that one in five Australians will develop depression at some stage in their lives. Therefore, the lifetime prevalence rate is generally taken to be in the order of 10–20%.13 However, it is necessary to note that the findings of individual studies vary considerably depending on the diagnostic tools implemented and the criteria used to define clinical depression. For example, the 2003 Australian National Survey of Mental Health and Well-being found the current prevalence rate of depression to be 3.2%.14 The prevalence rate of depression for both genders, as compared with other mental health disorders in Australia is given in Table 1.

Table 1 Prevalence rates of mental health disorders in Australian adults

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Population estimate</td>
</tr>
<tr>
<td>Any depressive disorder</td>
<td>4.2</td>
<td>275 300</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>7.1</td>
<td>470 400</td>
</tr>
<tr>
<td>Any substance use disorder</td>
<td>11.1</td>
<td>734 300</td>
</tr>
<tr>
<td>Any mental health disorder</td>
<td>17.4</td>
<td>1 151 600</td>
</tr>
</tbody>
</table>

Adapted from the study by Weissman et al.13
quality of life, exacerbation of coexisting illness, deliberate self-harm or suicide, premature death and overuse of health services, which all cost an estimated A$600 million per annum.\textsuperscript{15} Depression represents a significant disease burden in Australia, causing an average of 3.7 ‘healthy’ life years loss to the disability.\textsuperscript{15} The most recent Australian Burden of Disease study calculated the burden of mental disorders in Australia at 15% of the total, third in importance after heart disease and cancer, a proportion that further supports the public health importance of mental disorders.\textsuperscript{15} Table 2 shows the leading causes of disease burden in Australia in 1996. According to the Australian Health Insurance Commission 10.1 million prescriptions were written for antidepressant medication in 2003, with the SSRIs, such as fluoxetine (Prozac) and sertraline (Zoloft), accounting for greater than half of those prescribed.\textsuperscript{16}

### PATHOGENESIS

Mental illness is a multifactorial disease that can develop for many reasons. The contributing factors can be as wide-ranging as organic changes in the brain, environmental influences or genetic influences.\textsuperscript{9} Organic changes in the brain can be the result of alcohol abuse, drug-induced brain damage or altered production of neurotransmitters. Environmental influences affecting mental health can be as wide-ranging as the effects of stress, social isolation or major life events such as divorce, bereavement or redundancy. Genetically, some individuals may be predisposed to some types of mental illness. Depression is classified as a mood disorder of dysphoric nature, characterised by hopelessness, sadness and misery.\textsuperscript{9}

### CLINICAL FEATURES

The signs of depression fall into four main groups—mood disturbances, such as overwhelming sadness or guilt; behavioural changes, such as loss of interests; altered cognition and thought processes, such as a marked lack of concentration; and physical symptoms, such as weight loss and sleep disturbances.\textsuperscript{17} These symptoms may manifest themselves differently depending on developmental age. For example, depressed children may regress to an earlier stage of psychological functioning (e.g. a five-year-old child reverting to thumb-sucking and baby-talk), whereas depressed adolescents may exhibit oppositional and conduct disorders, including aggression, compulsive lying, high-risk sexual behaviours and truancy. Depressed middle-aged and elderly people, in contrast, are more likely to experience the physical symptoms, such as constipation and fatigue.\textsuperscript{17}

From a nutritional point of view, depression is usually accompanied by acute anorexia. There is a loss of interest in food and the pleasure of eating, as vividly described by the American novelist William Styron in his book \textit{Darkness Visible}, which gives an insight into his personal descent into depression—‘I found myself eating only for subsistence: food, like everything else within the scope of sensation, was utterly without savour’.\textsuperscript{5} Consequently, a serious feature is weight loss greater than 5% of total bodyweight or 3–4 kg over the past month.\textsuperscript{17}

### DIAGNOSIS

A number of structured interview formats incorporating specific investigative techniques and questions have been developed to aid in the assessment of depressed people, including the Structured Clinical Interview for DSM, the Structured Clinical Assessment for Neuropsychiatry, the Composite International Diagnostic Interview and the Diagnostic Interview Schedule.\textsuperscript{18} The severity of depression is assessed using rating scales designed for this purpose. Rating scales also serve as a tool for tracking the progress of treatment as they can be applied, with good repeatability, over the course of one or more therapies. Three of the most commonly used scales in current clinical practice are the Hamilton Depression Rating Scale, the Beck’s Depression Inventory and the Montgomery Asberg Depression Rating Scale.\textsuperscript{18}

There is no clear division between ordinary sadness, grief and clinical depression. Furthermore, no single diagnostic test can adequately diagnose depression and the nature of depression as a syndrome means that
diagnosis is based on a group of symptoms and observable physical and mental signs that commonly occur in conjunction. The only broadly identifiable distinction between generalised sadness, which is consolable and self-limiting, and depression is the prolonged period of time for which a lowered mood persists, and the incapacitating or disabling extent of the condition to the point where there is an inability to cope with the demands of everyday living. The criteria for diagnosing clinical depression, according to the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) are given in Table 3.

### RISK FACTORS

The accumulated evidence regarding the aetiology of clinical depression suggests that it is a complex disorder. Reference is often made to the bio-psychosocial model as an attempt to account for the interaction of biological, psychological and social factors involved in determining the liability to lifetime clinical depression. Biological factors arise from the physiology and biochemistry of body systems and function, as well as from genetic influences; psychological factors are derived from upbringing, emotional experiences and interpersonal interactions; and social factors result from a person’s cultural environment and current life situation.

### Criteria for a major depressive episode (DSM-IV)

Five of the most common symptoms of depression:

- Depressed mood (or irritable mood in children or adolescents) most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful)
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
- Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of bodyweight in a month), or decrease or increase in appetite nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- Recurrent thoughts about death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

<table>
<thead>
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<th>Gender and biological factors</th>
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Knowledge of neurotransmitter function provides an understanding of the biology of depression. Neurotransmitters are chemicals that are used to relay, amplify and modulate electrical signals between neurons and other cells. Neurotransmitters are broadly classified into small molecule transmitters or neuropeptides. The neurotransmitters implicated in depression and related conditions are the small molecule transmitters: dopamine, noradrenaline, adrenaline and serotonin. Within cells, these transmitter molecules are usually packaged in vesicles, so that when an action potential travels to a synapse, the rapid depolarisation causes calcium channels to open. Calcium then stimulates the transport of vesicles to the synaptic membrane, which then fuse, releasing the neurotransmitter. The receptor involved then determines the effect of the neurotransmitter. Imbalances of these neurotransmitters, dopamine, noradrenaline, adrenaline and serotonin are associated with mental illness.

Dopamine, noradrenaline and adrenaline are derived from the hydroxylation and decarboxylation of the amino acids tyrosine and phenylalanine in a common pathway consisting of several steps. These neurotransmitters are then metabolised to biologically inactive products through oxidation by monamine oxidase (MAO) and methylation by catechol-O-methyltransferase. Serotonin, 5-hydroxytryptamine is released specifically by cells in the brain stem and formed by the hydroxylation and decarboxylation of tryptophan. Normally, the hydrolase is not saturated, thus an increased uptake of tryptophan in the diet can increase brain serotonin content. Virtually all brain tryptophan is converted to serotonin. The serotonin concentration in the brain is far more sensitive to the effects of diet than any other monoamine neurotransmitter and can be increased up to 10-fold by supplementation in laboratory animals. These neurotransmitters are removed from the synaptic cleft by a reuptake mechanism that prevents the continued stimulation or inhibition of the post-synaptic neurone. Released serotonin is inactivated by MAO to form 5-hydroxyindoleacetic acid (5-HIAA).

Neurotransmitters have specific actions and are often targeted by prescription drugs, such as antidepressants as well as recreational drugs. Noradrenaline is a ‘feel good’ neurotransmitter, its release is enhanced by amphetamines, and removal from synapse is blocked by tri-cyclic antidepressants and cocaine. Dopamine is also a ‘feel good’ neurotransmitter, release is enhanced by L-dopa and amphetamines, reuptake is blocked by cocaine, it is deficient in Parkinson’s disease and it is thought to be involved in the pathogenesis of schizo-
phrenia. Serotonin is an inhibitory transmitter that plays a role in sleep, appetite, nausea, migraine headaches and regulation of mood. Drugs that block its uptake (Prozac) relieve anxiety and depression. Lysergic acid diethylamine (LSD) also blocks serotonin activity.22

Antidepressants are drugs that relieve the symptoms of depression. There are three main types: tricyclics (TCAs), MAOIs and reuptake inhibitors—SSRIs and SNRIs. Tricycles antidepressants derive their name from their three-ring structure. The therapeutic effects of antidepressants are believed to be related to an effect on neurotransmitters by inhibiting the monoamine transporter proteins of serotonin and noradrenaline.22 SSRIs specifically prevent the reuptake of serotonin, which increases the level of serotonin in synapses of the brain, whereas SNRIs slow down the reuptake of both serotonin and noradrenaline. MAOIs block the destruction of neurotransmitters by enzymes that normally metabolise them to an inactive form. TCAs prevent the reuptake of serotonin, noradrenaline and dopamine. The current mechanistic theory of action is that the long-term effect on modification of the neurotransmitter on receptors produces the antidepressant effect, not the short-term effect of a few days.22,23

There appears to be a strong genetic predisposition associated with the development of depression, as consistently shown in genetic epidemiological studies.24 Therefore, a positive family history is a powerful biological risk factor for depression. Five family studies of clinical depression have demonstrated its familial nature.18 A recent meta-analysis of these studies calculated the odds ratio for this relationship to be 2.84 (95% CI 2.31–3.49). Six twin studies have shown that genetic factors are highly significant in the development of depression, more so than individual-specific and shared environmental influences, such as general parenting style and background socio-demographic levels.18,25 Subsequently, the concordance rate is observed to be higher in identical twins than non-identical twins.25

Women are more vulnerable to mental illness at any age, with anxiety and depressive disorders predominating, although the male : female ratios change over lifespan.26 The female brain synthesises about two-thirds as much serotonin as the male brain.26 Men, in contrast, are more likely to suffer from antisocial personality disorder and drug and alcohol abuse.20 There are also gender differences in rates and expression of depression. Being female is a strong risk factor for depression, with women having twice the risk of men at any given age.13 Women between the ages of 18–34 years appear to be particularly at risk, with depression reaching a peak in young mothers. Family studies have discounted an X-chromosome-linked genetic transmission of depression.27 Research into female vulnerability shows the contributing effects of marital status, work and social roles, such as lack of a confidant, the presence of young children, lower socio-economic status and not working outside the home.27

Women experience their highest risk of having a depressive episode during pregnancy and following childbirth. Up to 70% of new mothers notice a transient change in their mood, usually describing themselves as being more anxious, tearful, irritable and emotional than normal, in the days following childbirth.28 This is sometimes referred to as the ‘postnatal or baby blues’, and this condition commonly resolves within a few days, when mothers are given appropriate support and reassurance from partners, family and friends. Given its widespread nature, ‘postnatal blues’ is often regarded as a normal psychological reaction to the accumulated stress associated with pregnancy and labour. This is in stark contrast to antenatal and postnatal depression, both of which require medical assessment, identification and possible treatment. Research suggests that the incidence and prevalence of antenatal depression are similar or equivalent to those of the postnatal period, with the rate of antenatal depression showing an increase in the past decade.29

Two possible explanations to account for this increase have been proposed. First, there is a tendency across all cultures to idealise pregnancy and as a result, the positive aspects of pregnancy are often overestimated.3 If and when the reality differs from expectations, a sense of disillusionment is felt, which may be one contributing factor to the development of antenatal depression.3 The second explanation concerns the rising age of first pregnancies in women in western societies and the seemingly ambivalent approach of the ‘modern’ women towards family planning and childbearing, possibly driven in part by various competing career and social demands.29 The clinical significance of antenatal depression lies in its potential to adversely affect the psychological preparation process of both mother and father-to-be in their adjustment to accommodate a new baby into their lives. Therefore, individual biology and genetic inheritance are both important factors to be considered in the development of antenatal depression.29

Postnatal depression affects between 10% and 15% of women in the first six months following childbirth.30 Because of its association with childbirth, it has been questioned as to whether postnatal depression is caused by hormonal changes. However, no definite link has been demonstrated with fluctuations in oestrogen or progesterone levels.31 Thus the aetiology of postnatal depression may have a psychosocial element as well. With regard to demographics, socially disadvantaged teenage mothers with poor social and emotional support networks appear to be at the highest risk of developing
postnatal depression. Adverse childhood experiences, such as sexual abuse and/or maternal deprivation, may add to the risk. Individual personality style also has an influence, in particular anxious, neurotic and overly sensitive traits. Women with histories of anxiety or depression are at higher risk, as are those who experienced antenatal depression. Traumatic obstetric difficulties during labour and delivery, such as high-forceps delivery or emergency Caesarean section, may lead to post-traumatic stress disorder, which may either resolve or evolve into postnatal depression.

Psychological factors

A person's style of thought and the way in which they interpret and react to life experiences may either protect or predispose them to mood disorders. Although clinical depression is now definitively refuted as being a 'character weakness', people with certain personality traits remain more vulnerable to developing depression. Two personality disturbances, which have been implicated as psychological risk factors for depression, are dependent and obsessional. People with dependent personalities submit to others and appear incapable of making decisions without considerable advice and approval. They transfer responsibility to others and are unable to work and live independently. Consequently, they often feel anxious and frightened when alone. This fear of being abandoned, coupled with a general lack of self-esteem, may explain the higher prevalence of depression in this group.

People with obsessive personalities exhibit an inflexible perfectionism, which interferes with their ability to complete everyday tasks. There is a preoccupation with rules, procedure and order, which results in great inefficiency and a loss of pleasure in accomplishment. Obsessive people often appear emotionally cold and judgemental and their need for control leads to long-term interpersonal difficulties. In addition, they required ideal standards are such that rarely do their own achievements measure up, creating much self-criticism and a gradual loss of self-confidence. This type of behaviour has obvious implications for the development of depression. Therefore, psychological functioning, including the complex issues of individual personality, temperament, problem-solving skills, values and personal resilience are aetiologically significant in clinical depression. Of particular relevance are the associations between the obsessive behaviours displayed in eating disorders and depression, as well as the link between the development of obesity and depression.

The association between depressive and eating disorders has been investigated in recent years following the observation that there appeared to be a high frequency of co-occurrence, whether it is prior to, simultaneously or subsequent to the development of the disorder. Prevalence of depression is higher in clinical samples because of referral and other biases (e.g. Berkson's bias—people suffering from more than one disorder are more likely to present for treatment), but even community-dwelling people with eating disorders, as identified in epidemiological surveys, have elevated rates of mood disorder compared with normal controls. Current rates for comorbid depression in specific subtypes of eating disorders are about 60% of people suffering from anorexia nervosa have been found to experience depressive episodes, with this figure increasing up to 90% for individuals with bulimia nervosa. The clinical significance of this comorbidity lies in the fact that deliberate self-harm and suicide risk may be elevated for people with concurrent eating disorders and depression. A meta-analysis of long-term outcome studies into anorexia nervosa estimated that up to half of the 5.6% mortality per decade of follow up was due to suicide in anorexia nervosa and depression.

The cause-and-effect relationship between eating disorders and depression is unclear. Starvation studies carried out during the Second World War provide evidence that food restriction in itself can lead to a lowering of mood. Therefore, there are a number of proposed theories that eating disorders may be merely an atypical presentation of an underlying depressive disorder, or that depression is a secondary mood disorder resulting from the physiological effects of food restriction and an extremely suboptimal bodyweight-for-height.

The observation that people of all ages and cultures turn to food as a source of comfort at times of emotional distress has led to the postulation of a link between depression and the development of obesity. Although it is recognised that to an extent, this reaction is normal and may indeed be a psychological technique used to adjust to or overcome the stresses, the long-term effectiveness of employing food as a coping strategy is questioned. Obesity, like depression, is the end result of interplay of many biological, psychological and social factors. Whether overeating associated with low mood leads to obesity is controversial; however, it may certainly be a contributing factor. In terms of co-occurrence, studies have found that the prevalence of depression in obese people is two to three times higher than in the general population.

Social factors

Clinical depression is usually preceded by a greater frequency of demanding life events. Acute adverse changes
in environmental and social circumstances appear to have an effect on the onset, maintenance and relapse of depression. Grief resulting from the experience of loss, whether that is of a loved one, a job, a diminution of social status or deterioration in health, is closely related to depression. In some cases, depression may be seen as a form of inappropriate and abnormal grief. The difference, however, lies in the observation that grief is a normal response to loss and as such is self-limiting and consolable in nature, whereas untreated depression persists and is unlikely to resolve independently.17

Chronic stresses, including long-term unemployment, marital/familial dysfunction and caring for an ail ing relative, may also precipitate or maintain a depressive episode. With regard to upbringing and childhood events, the experience of intra-familial sexual abuse, extended parental separations and a poorer perceived parental relationship appear to increase the risk of depression. Psychoanalytical theory advocates that as early life experiences are vital in the formation of personality, childhood psychological difficulties are closely associated with emotional disorders in later life. For example, disruptions in an infant’s relationship with its mother or other primary carer and the prolonged or recurrent absence of a mother-figure during childhood may lead to a greater vulnerability to depression in adolescence and adulthood.18

**MANAGEMENT**

**Pharmacological regimens**

Many patients with depression are successfully and effectively treated with antidepressant medication. These drugs fall into three main groups—the TCAs, MAOIs and SSRIs and SNRIs.22 Of particular importance to the present review is the mode of action of such antidepressant medications, from which stems the potential for nutritional manipulation as an adjunct to conventional drug treatment and psychotherapy. Research investigating the links between dietary components and depression explores the multiple mechanisms through which nutrients can act in similar ways to antidepressant drugs.11

All antidepressants act by increasing the availability of the monoamine neurotransmitters—serotonin, noradrenaline or dopamine—at the synaptic junction. The monoamine reuptake pump terminates the action of these released neurotransmitters once the electrical impulse has been transmitted. SSRIs and SNRIs selectively and relatively powerfully block presynaptic serotonin or noradrenaline reuptake, whereas TCAs block the general reuptake of monoamines more weakly. MAOIs inhibit the monoamine oxidase enzyme that metabolises the monoamine neurotransmitters, allowing for longer-lasting action of each released neurotransmitter. Antidepressant medications have a number of side effects, as shown in Table 4.17 Short-term use leads to an increase in neuronal firing, whereas longer-term use leads to the downregulation of neuronal firing, for example, the use of an SSRI for four to six weeks is associated with the downregulation of serotonergic transmission.22 Patients prescribed MAOIs are given strict dietary restrictions on foods, beverages and other medications containing the naturally occurring amino acid, tyramine, to reduce the risk of hypertensive crises.4 The symptoms characteristic of this rapid rise in blood pressure are severe headache, chest pain, palpitations, neck stiffness and possible intracranial haemorrhage and death. A list of restricted foods is given in Table 5.4

| **Table 4** Common side effects of antidepressant medication |
|------------------|------------------|------------------|------------------|------------------|
| **Gastrointestinal** | **Cardiovascular** | **CNS** | **Sexual** | **Anticholinergic**(a) |
| Anorexia | Prolonged bleeding time | Headache | Loss of libido | Dry mouth |
| Nausea and vomiting | Orthostatic hypotension | Agitation, restlessness, | Impotence/erectile | Blurred vision |
| Weight loss or gain | Tachycardia | anxiety | difficulties | Urinary retention |
| Diarrhoea/constipation | Slowed cardiac conduction | Insomnia/somnolence | Ejaculatory failure/ | Delirium/dizziness |
| | | Tremor, sweating | premature ejaculation | |
| | | Muscle weakness | Fatigue | |
| | | Anorgasmia | | |

(a) Relevant to tricyclic antidepressants.
CNS = central nervous system.
Adapted from the study by Bloch and Singh.17

Adjunctive nutritional regimens

There has been an association between depression and nutrition since the first emergence of mood disorders. In the late 19th century, Krafft-Ebing exerted great influence on the thinking about depression (then known as
melancholia) with his famous work Textbook of Psychiatry (1879), in which the illness is described as being due to ‘an abnormal condition of the psychic organ dependent upon a disturbance of nutrition’.38,39 This association has persisted over the centuries and is now reflected in the great deal of research investigating the links between dietary components and the development and treatment of depression. The majority of the research explores the biological changes seen in depression and the potential for nutrients to exert beneficial effects on modulating or correcting such biochemical imbalances.

As the understanding of the neurobiology of depression expands, the theories relating nutrition to depression similarly increase.

There are multiple mechanisms by which nutrients can have an effect on the development, maintenance and relapse of depression. Nutritional factors such as n-3 PUFAs, n-6 to n-3 PUFA ratio, luteine, tryptophan, vitamin B6, B12, SAMe and Hypericum perforatum (St John’s Wort) and various cofactors in enzyme systems may influence depression by the modulation of neuronal membrane fluidity with resulting changes in neuronal uptake and binding, action of nutrients as neurotransmitter substrates or initiation of neurotransmitter receptors.41,42,43

Table 5 Foods and beverages prohibited when taking monoamine oxidase inhibitors

<table>
<thead>
<tr>
<th>Foods and beverages with a high tyramine content:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Banana, banana-flavoured desserts, banana chips</td>
</tr>
<tr>
<td>• Broad bean pods</td>
</tr>
<tr>
<td>• Sauerkraut</td>
</tr>
<tr>
<td>• Matured and aged cheeses</td>
</tr>
<tr>
<td>• Aged meat or liver products (e.g. pate, foie gras), dry sausage (e.g. salami), smoked or pickled fish</td>
</tr>
<tr>
<td>• Soy and soy products (e.g. miso, tofu)</td>
</tr>
<tr>
<td>• Yeast-based spreads (e.g. Vegemite, Marmite, Promite)</td>
</tr>
<tr>
<td>• Protein shakes, red wine, beer</td>
</tr>
</tbody>
</table>

Adapted from the study by Garrow and James.7

A 1995 review promotes the hypothesis that a deficiency in n-3 PUFA is of aetiological importance in the development of depression.10 Epidemiological data show the trend in decreasing dietary n-3 PUFA consumption and the increasing incidence of depression, both over time and between nations.10,42 Further investigation suggests that the significance may lie in the increase in n-6 to n-3 ratio, rather than simply low omega-3 intake alone, as these two fatty acids compete for incorporation into cell membranes,41,42 and further desaturation. A high n-6 diet therefore prevents the incorporation of n-3 PUFA into cell membrane phospholipids,40 which may lead to decreased membrane fluidity and impaired cell signalling. An imbalance between n-6 and n-3 PUFA intake also has harmful effects on the cardiovascular system—the predisposition of vascular cells to lipid peroxidation47 and the reduced endogenous production of apoprotein A-I, mean lower HDL-cholesterol levels, less reverse cholesterol transport and consequently, a higher risk of atherosclerosis.48 The pro-inflammatory effects of a diet excessively high in n-6 PUFA have been
implicated in the development of a number of joint conditions, most notably arthritis.69 The change in n-6 to n-3 PUFA ratio of dietary intake is highlighted when comparison is made between the Palaeolithic diet and the current western way of eating. Anthropological information suggests that the intake of n-6 and n-3 PUFA during the Palaeolithic era was roughly equal, whereas the present n-6 to n-3 PUFA ratio in western countries has been estimated to be between 10 and 25 to 1.10,50 The n-6 to n-3 PUFA imbalance has been due mainly to the increase in vegetable and seed oil use, and a decrease in fish or fish oil intake. Data from the 1995 National Nutrition Survey estimates suggest that the n-6 to n-3 PUFA ratio to be 15 to 1 in the Australian diet, which would preclude the incorporation of n-3 PUFA into membrane phospholipids.51

Direct evidence of a role for n-3 PUFA in depression is provided by a number of studies, which examined the fatty acid compositions of erythrocyte membranes, serum cholesteryl esters and phospholipids. Two major studies in this area, carried out between 1996 and 1999, found that in the analysis of results of a study that depression is associated with: significantly decreased total n-3 PUFA, increased monounsaturated fatty acid proportions and increased n-6 to n-3 PUFA ratio, more specifically, arachidonic acid to EPA ratio, in cholesteryl esters and phospholipids.52,53 A supporting study, carried out in 1998, also found a significant depletion in total n-3 PUFA, and in particular DHA, in the erythrocyte membranes of depressed patients.54 In 1998, the strong correlation between a low dietary intake of n-3 PUFA, n-3 PUFA content of erythrocyte membranes and the severity of depression was further elucidated.55 Analyses of the results of biochemical studies suggest that omega-3 PUFA increases CSF 5-HIAA, with resulting improvements in depressive symptoms.56 Depressed subjects have also been found to have low CSF concentrations of serotonin, 5-hydroxytryptamine or have impairments in serotonin metabolism.23

Membrane fluidity refers to the state of the fatty acid chains comprising the lipid bilayer microstructure of cell membranes.57 In general, an optimal state exists where the physical properties of the cell membrane are most conducive to its biological function. In neuronal membranes, this relates to: secretion of neurotransmitters, effective neurotransmitter binding and intracellular signalling, and production of secondary messengers, ion channel function, receptor function, enzyme activity and gene expression. Omega-3 PUFA are essential components of the lipid bilayer in such membranes and a deficiency may adversely affect the signalling pathways in neurones. There is a growing body of evidence, which consistently suggests that membrane lipid abnormalities occur in depression. Omega-3 PUFA, in particular DHA, is depleted in depressed subjects.52–55,57,58

An analysis of recent research findings linking physical and mental illness has highlighted the cause-and-effect relationship of cardiovascular disease and depression. A meta-analysis of 83 studies showed that depression correlated highly significantly with coronary artery disease and myocardial infarction,59 depression being the strongest psychological predictor of coronary heart disease. In addition, patients with lowered mood have a worse prognosis following a cardiac event.60 Although there is a growing body of literature on the role of fish and fish oil consumption in depression—most of which report results from epidemiological and observational studies—clinical experimental data in this area remain scarce. To date, there have been only a small number of well-designed and executed trials conducted in this area. An evaluation of the omega-3 fatty acid DHA as an alternative to pharmacological treatment of major depression involving 35 depressed subjects failed to show a significant effect of DHA monotherapy.61 In another study, the ethyl ester of the omega-3 fatty acid EPA (E-EPA) was investigated. At a dose of 200 mg/day, and as an adjunct to usual antidepressant treatment, E-EPA reduced symptoms of depression, as measured by the 24-item Hamilton Depression Rating Scale.62 However, whether the antidepressant effect of this specific omega-3 PUFA can be translated to encompass the broader omega-3 family cannot be determined by that study. The dose-range response of EPA was investigated in a larger study involving 70 depressed subjects. Significant improvements in mood were observed in the intervention group receiving 100 mg of EPA, but not at higher doses.63 The phenomenon of a ‘threshold’ once optimal omega-3 PUFA dose is reached is also seen in rheumatoid arthritis trials, where a higher dose of omega-3 PUFA did not result in further improvements in end measures.64 The final study used both EPA and DHA as an intervention, with results after the eight-week trial showing highly significant improvements in depressive symptoms.65

It is clear that the research area of diet and brain function is in a relatively early stage and as yet, there have been no therapeutic values defined for the optimum dose of omega-3 PUFA for the alleviation of negative symptoms associated with depression.66 Therefore, the safest and most sensible approach to take when considering omega-3 PUFA supplementation may be to follow the recommendations set for optimum PUFA intake for cardiovascular health. The American Heart Association,67 the European Society for Cardiology,68 the Scientific Advisory Committee on Nutrition (UK),69 the National Health and Medical Council70 and The
influences the conversion to serotonin. When tryp- 
tophan availability to the brain neurotransmitter, serotonin. Many studies have demon-
strated that the optimal omega-6 to omega-3 ratio may vary according to the disease and disease severity. Until more extensive trials of omega-3 PUFA and depression have been conducted, the above recommended intakes should be considered as the levels associated with a general healthy diet and/or potential supplementation.

The amino acid tryptophan is the precursor to the neurotransmitter, serotonin. Many studies have demonstrated that the tryptophan availability to the brain influences the conversion to serotonin. When tryptophan is administered as a supplement or is derived from a meal, it increases the amount of tryptophan available to serotonin neurons. This availability can rapidly increase serotonin production to enhance serotonin release in neurons that are rapidly firing. The effect of readily available tryptophan through supplementa-
tion or meal manipulation can change sleep and mood patterns. The effects are small compared with the effects of potent drugs, which enhance serotonin function in the brain. As with many dietary regimens, a dichotomous paradigm of nutritional therapy and pharma-
cotherapy as used in the treatment of diabetes and cardiovascular disease has much to recommend it.

Wurtman et al. suggest that high-carbohydrate meals increase serotonin synthesis. Consumption of a meal that is high in carbohydrate, branched chain amino acids and tryptophan has a significant effect because both glucose from the carbohydrate and the branched chain amino acids (particularly leucine) increase insulin secretion. Insulin facilitates the transport of branched chain amino acids into muscle cells, thereby reducing the competition for tryptophan by the large neutral amino acids for the tryptophan transporter protein to carry it across the blood–brain barrier. Drowsiness induced by increased serotonin is the common effect of a large carbohydrate meal.

A number of other nutritional factors, mainly in relation to micronutrients, amino acids and herbal remedies, have been proposed in the development, maintenance and relapse of depression. The possibility of clinical and subclinical nutritional deficiencies in depressed patients has been raised following the suggestion that this group may have physiological requirements for certain nutrients above and beyond the recommended dietary intake. Several studies have found that there is an increased incidence of folate deficiency in psychiatric patients, especially in those with severe depression with up to one-third having suboptimal folate status. Whether this widespread deficiency is a result of chronic low folate intake or a compromised folate metabolism is unclear. However, one of the most common clinical features of depression is a diminished interest in food. This, accompanied with a generalised lassitude and a withdrawal from social interactions, may lead to poor dietary intake and impaired nutritional status. Morris et al. recommend that a folate supplement may be important during the year following a depressive episode.

Despite an increasing body of research, the associations between B12, B6, folate and SAMe and treatment outcomes in depressive disorders are still unsolved and much of this body of research has produced conflicting results. Low concentrations of folate and B12 may impair methylation reactions and both nutrients are necessary for methionine synthesis and the subsequent formation of SAMe, the universal methyl donor, important in the formation of neurotransmitters and phospho-
lipids. Culturally defined dietary habits may influence the relationship between folate status and depression in different societies where a low folate level was not detected in Chinese patients or Latino men, but in Latino women. Tolmunen et al. reported that low dietary folate and depressive symptoms are associated in middle-aged Finnish men. The association between folate and depression may be more prominent in elderly subjects, among whom folate deficiency has been relatively common in some studies. Hintikka et al. demonstrated that higher B12 levels are significantly associated with better outcomes in young and middle-aged subjects, but further studies were warranted. Because the metabolite of vitamin B6, pyridoxal 5′-phosphate is a coenzyme in the tryptophan-serotonin pathway, a lack of B6 might theoretically cause depression, despite being readily available in a balanced diet. Penninx et al. found that individuals with a B12 deficiency had a twofold risk of severe depression. Bottiglieri et al. reported that depressed patients had increased plasma homocysteine. Low folate status was found in depressed individuals in the general...
population of the USA and the response to antidepressants poorer in patients with a low folate status. Hvas et al. in a study of an elderly population suggest that B₆ plays a role in developing symptoms of depression with a significant association between the B₆ derivative pyridoxal 5'-phosphate and symptoms of depression. The mechanism of antidepressant effect involved in B₁₂, B₆, folate and SAMe may well be mediated through homocysteine and/or the synthesis of monoamines in the brain. The higher rates of depressive disorders in subjects with low folate and high homocysteine levels are due to differences in cardiovascular factors and physical comorbidity. Serum folate is more sensitive to nutritional intake than vitamin B₁₂ and folate deficiency can be a consequence of loss of appetite.

The antidepressant mechanism of SAMe has not been elucidated; however, it is known that SAMe exerts a stimulatory effect on monoamine metabolism and turnover. SAMe treatment increases the concentration of 5-HIAA. Two mechanisms have been proposed; the stimulatory effect on monoamine transmitters or alternatively increased or restored membrane phospholipids methylation. SAMe, through its activity as a methyl donor, has the ability to increase the fluidity of cell membranes by stimulating phospholipids methylation. The effect of SAMe on receptor systems is interesting because the evidence suggests that age-related changes in the membrane environment may result in increased membrane viscosity and thus membrane dysfunction.

St John's Wort is an herbal extract derived from the plant Hypericum perforatum. It has been extensively studied in Europe, particularly in Germany, where it is as commonly recommended in the treatment of depression as Prozac (fluoxetine) is in the USA. An early meta-analysis of 23 randomised control trials of the efficacy of St John's Wort in the treatment of depression indicated that there was a therapeutic benefit. Of the 23 clinical trials, 20 were double-blinded in study design, and there were 1757 test subjects, with differing severities of depression. The subjects received one of the following interventions: herbal supplement of St John's Wort (dose range from 200 mg to 1800 mg per day), a traditional antidepressant drug or a placebo, for four to eight weeks. In 13 of the trials, St John's Wort resulted in a 55% alleviation of depressive symptoms, compared with 22% for placebo. The difference was less in the three trials comparing St John's Wort with antidepressant drugs; however, the additional advantage of a significant reduction in adverse side effects was noted. This 1996 review reported that St John's Wort was not only better tolerated than the commonly prescribed antidepressant medications; it was also more effective in the alleviation of negative symptoms associated with depression. However, the analysis of the results of two large clinical trials carried out more recently in the USA do not support the views expressed in the 1996 review. Gupta and Moller suggest that the reasons for differences in study findings are related to St John's Wort interactions with prescribed medications and patients taking both should be closely monitored.

**CONCLUSION**

The World Health Organization estimates that major depressive disorders will become the second leading cause of morbidity worldwide by the year 2020. Fortunately depression is a treatable condition. Successful management of depression involves pharmacological and psychotherapeutic treatments. As is common today, chronic diseases such as diabetes mellitus, cardiovascular disease and some musculoskeletal disorders have a dichotomous treatment paradigm in which nutritional regimens have an adjunctive treatment role with pharmacotherapy. There are many promising candidates for nutritional adjuvant treatment for depression, n-3 PUFAs and the phospholipid hypothesis are the most promising. However, tryptophan, vitamins B₆, B₁₂, folate and SAMe also demonstrate promise in contribution to the phospholipid methylation hypothesis. Despite the increasing body of research, differences in dietary cultures, stages in the human life cycle and comorbidities all cloud the issues involved. Optimistically, the role of balanced nutrition should be recognised and then nutrition and specific nutrients will be used as adjuvant treatment in the maintenance of good mental health.

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