Dysregulated biological pathways in major depression

An examination of the antidepressant effects of curcumin

by
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Signed statement by research candidate

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

I hereby certify that this thesis is submitted in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author; attesting to my contribution to the joint publications (appendix 2).

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Abstract

Major depression is associated with multiple dysregulated biological pathways which are influenced by an array of lifestyle, psychological, environmental and biological factors. Nutraceuticals including curcumin, derived from the Indian spice turmeric, also have the potential to influence these depressogenic pathways. Consequently, the aims of this thesis were to:

1. Review and integrate research on dysregulated biological pathways, namely those associated with neurotransmitter imbalances, immuno-inflammatory processes, hypothalamus-pituitary-adrenal axis dysregulation, oxidative and nitrosative stress, mitochondrial dysfunction and neuroprogression.
2. Review research on the relationship between several lifestyle-based factors and depression, and examine their effects on these depressogenic pathways. More specifically, the influence of diet, exercise, sleep, vitamin D, omega 3 essential fatty acid deficiency, stress and trauma, obesity and smoking were appraised along with their potential to prevent and treat major depression. The influence of psychological and pharmaceutical interventions on these dysregulated biological pathways was also reviewed.
3. Examine the antidepressant effects of curcumin. In animal-based models, curcumin has demonstrated antidepressant effects, although clinical studies are lacking. The efficacy of curcumin in an 8-week, randomised, double-blind, placebo-controlled study was examined in people with a major depressive disorder. Curcumin at a dose of 500 mg, twice daily, was compared with a placebo. The Inventory of Depressive Symptomatology-Self Report ($IDS\text{-}SR_{30}$) and Spielberger State-Trait Anxiety Inventory were used to assess symptomatic change. Curcumin and placebo were equally effective in lowering depressive

and anxiety symptomatology from baseline to week 4, but from weeks 4 to 8 curcumin supplementation was associated with superior antidepressant efficacy.

4. Review the potential role of peripheral biomarkers in major depression and examine biomarker changes following curcumin supplementation. Measurement of peripheral biomarkers has the potential to enhance diagnosis, evaluate treatment progress and facilitate treatment matching. In a randomised, double-blind, placebo controlled study, the influence of curcumin on several urinary, plasma and salivary peripheral biomarkers was examined. The efficacy of biomarkers to predict treatment efficacy from curcumin administration was also examined. Urinary leukotriene B4, thromboxane B2 and substance P were associated with changes following curcumin treatment, while higher baseline concentrations of plasma endothelin-1 and leptin were associated with greater treatment efficacy.

Limitations associated with the clinical studies are reviewed and recommendations for future research are provided.

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List of publications included as part of this thesis

1. Lopresti, A.L., Hood, S.D., Drummond, P.D. (2013) A review of lifestyle factors that contribute to important pathways associated with major depression: diet, sleep and exercise. Journal of Affective Disorders, 148(1):12-27. (Chapter 3)
2. Lopresti, A.L. & Drummond, P.D. (2013) Obesity and psychiatric disorders: commonalities in dysregulated biological pathways and their implications for treatment. Progress in Neuropsychopharmacology and Biological Psychiatry, 45:92-9. (Chapter 3)
3. Lopresti, A.L., Hood, S.D., Drummond, P.D. (2012) Multiple antidepressant potential modes of action of curcumin: a review of its anti-inflammatory, monoaminergic, antioxidant, immune-modulating and neuroprotective effects. Journal of Psychopharmacology, 26(12):1512-24. (Chapter 4)
4. Lopresti, A.L., Maes, M., Maker, G.L. Hood, S.D., Drummond, P.D. (2014) Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study. Journal of Affective Disorders, 167:368-375. (Chapter 5)
5. Lopresti, A.L., Maker, G. Hood, S.D., Drummond, P.D. (2014) A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers. Progress in Neuropsychopharmacology and Biological Psychiatry, 48:102–111. (Chapter 5)
6. Lopresti, A.L., Drummond, P.D. (2014) Saffron *(Crocus Sativus)* for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action, Human Psychopharmacology: Clinical and Experimental (accepted for publication) (Appendix 1)

All publications have undergone a peer review process. Further details about relevant journals are included in appendix 3

The following empirical study has been submitted to a peer reviewed journal and is currently being reviewed and considered for publication:

7. Lopresti, A.L., Meddens, M., Maes, M., Maker, G.L., Arnoldussen, E., Drummond, P.D. (2014) Curcumin and major depression: peripheral biomarkers to predict treatment response and antidepressant mechanisms of change (Chapter 5)

Contents

Abbreviations

5HT, serotonin
ACTH, adrenocorticotropic hormone
ATP, adenosine triphosphate
BDNF, brain derived neurotrophic factor
BH4, tetrahydrobiopterin
CBT, cognitive behaviour therapy
CMI, cell-mediated immunity
COX-2, cyclooxygenase-2
CRP, C-reactive protein
CRH, corticotropin-releasing factor
CNS, central nervous system
CSF, cerebrospinal fluid
DHA, docosahexaenoic acid
ET-1, endothelin 1
EFA, essential fatty acid
EPA, eicosapentaenoic acid
GR, glucocorticoid receptor
HPA, hypothalamus-pituitary-adrenal
IDO, indoleamine 2,3 dioxygenase
IL, interleukin
IFN, interferon
KYN, kynurenine
KYNA, kynurenic acid
LTB4, leukotriene B4
LPS, lipopolysaccharide
MOAIs, monoamine oxidase inhibitors
MRI, magnetic resonance imaging
NOX2, NADPH oxidase
NO, nitric oxide
PTSD, post-traumatic stress disorder
O&NS, oxidative and nitrosative stress
QUIN, quinolinic acid
ROS, reactive oxygen species
RNS, reactive nitrogen species
SES, socioeconomic status
SERT, serotonin transporter
SNRIs , serotonin-noradrenaline reuptake inhibitors
SSRIs, serotonin reuptake inhibitors
sIL-2R, IL-2 receptor
SUB-P, substance P
Tbx-2, thromboxane B2
TCAs, tricyclic antidepressants
TDO, tryptophan 2,3-dioxygenase
TRYCATs, tryptophan catabolites along the IDO pathway
TNFα, tumor necrosis factor alpha

Chapter 1:
Introduction

Major depressive disorder affects one in seven Australians sometime in their life, with greater rates in women (17%) compared to men (10%) (Australian Bureau of Statistics., 2009). The World Health Organisation (WHO) has predicted that by 2030, depression will account for more disability than any other physical or mental disorder throughout the world (WHO, 2008).

Currently, major depressive disorder is treated primarily through pharmacological and/or psychological interventions. Pharmacological interventions mainly comprise serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs) and, to a lesser extent, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MOAIs). From a psychological perspective, cognitive-behaviour therapy (CBT) is frequently utilised by mental health practitioners.

On the whole, these interventions have comparable efficacy for the treatment of major depression (Cuijpers et al., 2013b). From several meta-analyses examining antidepressant therapies, it has most consistently been concluded that they have reasonable efficacy in treating moderate and severe depression but have minimal benefit for the treatment of mild depression (Kirsch et al., 2008; Undurraga and Baldessarini, 2012). For example, Fournier *et al.* (2010) concluded that the magnitude of benefit from antidepressant medication compared with placebo increased with the severity of depressive symptoms, but antidepressant medication had minimal or non-existent benefit in patients with mild or moderate symptoms. For patients with very severe depression, the benefit of medications over placebo was substantial.

CBT consists of several variations including traditional CBT, and third-wave cognitive behavioural therapies such as acceptance and commitment therapy, dialectical behaviour therapy and functional analytic psychotherapy. In a recent meta-analysis it was concluded that these variations were similarly effective for the treatment of major depression (Hunot et al., 2013). From a meta-analysis examining all forms of CBT with placebo, it was concluded that CBT had an effect size of 0.71 (Hedges g), although this level was significantly reduced (Hedges g = 0.53) when only high-quality studies were included in the analyses (Cuijpers et al., 2013a).

Combined treatments incorporating both psychological and pharmacotherapy have greater rates of efficacy compared to stand-alone treatments. In a recent meta-analysis, the overall effect size in favour of combined treatments (incorporating pharmacotherapy and psychotherapy) compared to pharmacotherapy alone for the treatment of depression and anxiety was 0.43 (95% CI: 0.31-0.56), indicating a moderate magnitude of efficacy (Cuijpers et al., 2014). The effects of combined treatment compared with placebo were about twice as large as those of pharmacotherapy compared with placebo, underscoring the clinical advantage of combined treatment.

While psychological, pharmacological and combined treatments have proven to be helpful for many people with major depression, their efficacy is far from perfect and efforts to improve response rates over the past decade have been disappointing. In a *post hoc* analysis of the Sequenced Treatment Alternatives to Relieve Depression trial data, it was found that 90% of patients who achieved remission from antidepressant treatment had at least one residual symptom (Nierenberg et al., 2010). This is significant as residual symptoms are predictive of relapse, even among those who meet the criteria for remission (Judd et al., 2000; Paykel et al., 1995).

Incomplete symptom resolution and treatment resistance may partly be due to the significant heterogeneity associated with major depressive disorder. While major depression comprises a constellation of symptoms detailed in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), there is significant variability in reported symptoms. For example, appetite changes can comprise either hypo- or hyperphagia, sleep disturbances involve insomnia or hypersomnia, and weight can change in either an upward or downward direction. There is also significant variability in reports of fatigue, suicidal ideation, and anhedonia. The high comorbidity of depression with cardiovascular, metabolic and digestive illnesses is also likely to influence treatment outcome (Katon, 2011).

Several solutions have been proposed to enhance treatment success. These include subtyping depression based on (1) symptoms (e.g., melancholia, psychotic depression, atypical depression and anxious depression); (2) aetiology (e.g., adjustment disorders, early trauma depression, reproductive depression, perinatal depression, organic depression and drug-induced depression); (3) time of onset (e.g., early and late onset depression, and seasonal affective disorder); (4) gender; and (5) treatment resistance (Baumeister and Parker, 2012). While research on depression subtyping continues, some findings have been promising (Baumeister and Parker, 2012). For example, melancholic depression is associated with greater treatment efficacy from antidepressant medication (Yang et al., 2013).

Biological assessments have also been used to increase understanding of the mechanisms associated with depression and to facilitate treatment matching. For example, there has been increasing interest in genetic testing to assist decision making around options for antidepressant treatment (Tansey et al., 2012; Uher et al., 2013). Genetic testing is still in its infancy but so far has been disappointing (Uher et al., 2013). The use of peripheral biomarkers, such as those associated with oxidative and nitrosative stress (O&NS), inflammation, monoamine activity, neuroprogression and neuroendocrine activity, have also been

investigated to identify depressive subtypes and to improve treatment matching (Lopresti et al., 2014; Schmidt et al., 2011). The clinical application of biomarkers is still in an early stage but has provided initial clues into treatment resistance from antidepressant (Eller et al., 2008; Lanquillon et al., 2000) and psychological therapies (Harley et al., 2010).

As a result of only moderate success in the treatment of major depression, interest in alternative treatment options has increased. This has included investigations into the potential of pharmaceutical anti-inflammatory agents such as acetyl-salicylic acid and cyclooxygenase-2 (COX-2) inhibitors to enhance treatment outcome (Abbasi et al., 2012; Berk et al., 2013; Fond et al., 2014). The use of COX-2 inhibitors has shown some promise in enhancing treatment response and remission rates (Fond et al., 2014).

There has also been interest in applying various nutraceuticals for the treatment of depression (Sarris et al., 2011). In the domain of mental health, natural and complementary therapies are a popular option sought by the general community. For example, in a sample of women with depression, 54% of respondents reported using complementary and alternative medicine over the past year. More specifically, 20% of the sample reported using herbal therapies, while 16% used vitamins and nutritional supplements to help overcome mental and physical ailments (Wu et al., 2007). In another study on participants being treated for depression, 63% of respondents reported taking at least one dietary supplement within the previous 12 months. On average, supplement users took 2.8 dietary supplements during the assessment period (Silvers et al., 2006).

Research on nutraceuticals, such as St John's wort (Rahimi et al., 2009), S-adenosylmethionine (Papakostas et al., 2012), omega-3 fatty acids (Grosso et al., 2014), folate (Taylor et al., 2004) and saffron (Hausenblas et al., 2013; Lopresti and Drummond, 2014), have shown them to be promising stand-alone or adjunct treatments for depression.

As a result of increasing interest in natural therapies and the role of biomarker identification in major depression, the aims of this PhD were to:

1. Review dysregulated biological pathways associated with major depression, namely those associated with inflammation, oxidative and nitrosative stress, neurotransmitter imbalances, hypothalamus-pituitary-adrenal (HPA) axis regulation and neuroprogression. This is detailed in Chapter 2 and in two published papers.
2. Review the relationship between depression and several lifestyle factors; and through a literature review examine their potential influence on these depressogenic pathways. Stress and trauma, omega-3 deficiency, vitamin D deficiency and smoking are covered in Chapter 3. The role of diet, exercise, sleep and obesity are detailed in two published papers.
3. Through a literature review, summarise the influence of psychological therapies and pharmacological antidepressants on these depressogenic pathways. This is covered in Chapter 4.
4. Review the influence of curcumin on these dysregulated biological pathways, which is detailed in a published paper included in Chapter 5.
5. Review research on peripheral biomarkers associated with immuno-inflammation and oxidative stress in major depression, and examine the potential of these markers to assess treatment response and facilitate treatment matching. This is covered in a published paper included in Chapter 6.

The following hypotheses were investigated in a randomised, double-blind, placebo controlled trial:

1. Curcumin is an effective antidepressant for the treatment of mild-to-moderate major depressive disorder (examined in a published paper included in Chapter 5).

2. The antidepressant mechanisms associated with curcumin can be evaluated through pre- and post-collections of peripheral biomarkers (examined in an unpublished paper included in Chapter 6).
3. Curcumin will have greater antidepressant efficacy for specific subgroups of individuals with major depressive disorder. These subgroups can be identified through symptomatic profiles (e.g., atypical depression) and/or baseline biomarker concentrations. This has the potential to facilitate treatment matching and therefore increase treatment success rates (examined in papers included in Chapters 5 and 6).

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Chapter 2:
Biological mechanisms associated with major depression

Several dysregulated biological mechanisms are associated with major depressive disorder. These include those associated with neurotransmitter disturbances, immuno-inflammatory processes, HPA axis dysregulation, O&NS, mitochondrial dysfunction and neuroprogression. These depressogenic pathways are strongly interconnected, further exacerbating dysregulations or buffering against further disturbances. Each of these pathways, detailed in Figure 1, are described in the following sections.

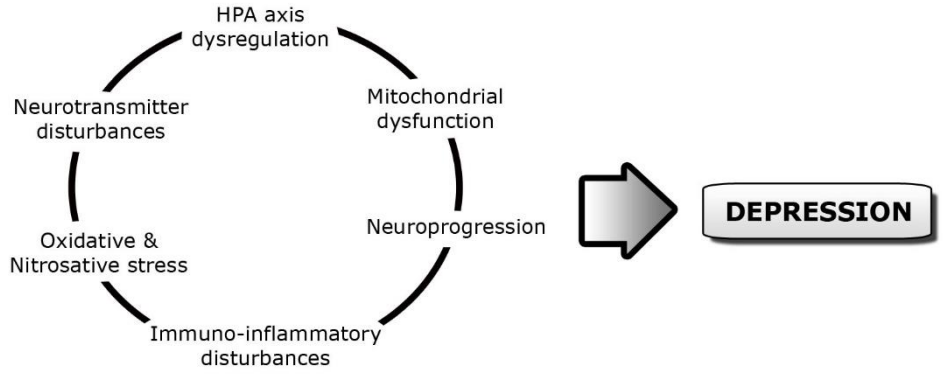

Figure 1. *Biological pathways associated with major depressive disorder.* Several biological pathways are associated with major depressive disorder. These pathways are strongly interconnected, up- or down-regulating further activity.

Neurotransmitter disturbances

A review of research on neurotransmitter disturbances in major depression is covered in published papers comprising Chapters 3 and 4 (Lopresti et al., 2012; Lopresti et al., 2013), and therefore will not be repeated here. However, an overview demonstrating the influence of monoaminergic activity on other dysregulated pathways is outlined below.

Monoaminergic activity and its relationship with depressogenic pathways

A bi-directional relationship likely exists between monoaminergic activity and several depressogenic pathways. For example, mechanisms associated with serotonin metabolism including receptor density and sensitivity, and the availability of serotonin transporter (SERT), influence brain-derived neurotrophic (BDNF) concentration and expression (Calabrese et al., 2013; Homberg et al., 2014). Serotonin also influences HPA activity by modifying the secretion of corticotropin-releasing factor (CRH), adrenocorticotropic hormone (ACTH) and cortisol, and impacts on glucocorticoid receptor (GR) sensitivity (Calogero et al., 1990; Griffiths et al., 2012; Jorgensen, 2007). While inflammation and cytokine production influence serotonin activity, the reverse is also true. That is, serotonin is also involved in the modulation of cytokine production (Cloez-Tayarani et al., 2003; Durk et al., 2005). Serotonin also protects against mitochondrial death (Zhou et al., 2014). The neurotransmitter noradrenaline also influences several of these depressogenic pathways. For example, it inhibits lipopolysaccharide (LPS)-induced cytokine production (Goyarts et al., 2008), and provides neuroprotection against oxidative stress (Jhang et al., 2014).

Immune-inflammatory dysregulation

The immune response, which consists of the innate and adaptive systems, is an essential response to the presence of infection, cellular damage and stress. The innate immune system is the first line of defence and comprises cells and other mechanisms that defend the host from infection in a non-specific manner. The adaptive immune system, also known as the acquired immune system, comprises highly specialised, systemic cells and processes that eliminate or prevent pathogen growth. Adaptive immunity creates immunological memory after an initial response to a specific pathogen, leading to an enhanced response to subsequent encounters with that pathogen (Huether and McCance, 2004).

Both the innate and adaptive systems include humoral and cell-mediated immunity (CMI). Humoral immunity, also referred to as the antibody-mediated immune system, is the aspect of immunity that is mediated by macromolecules such as antibodies, complement proteins and certain antimicrobial peptides found in extracellular fluids (Huether and McCance, 2004). CMI entails the interaction between different immune cells, such as T lymphocytes and macrophages/ monocytes that do not involve complement proteins, the acute phase response or antibodies (Leonard and Maes, 2012).

While essential for survival, several diseases, including major depressive disorder, are characterised by an inappropriate immune-inflammatory response. This is supported by the following observations:

1. The prevalence of major depression is increased in people with inflammatory-related medical conditions.
2. Major depressive disorder is associated with increased markers of inflammatory and immune responses.
3. Anti-inflammatory agents are beneficial for the treatment of major depression.
4. Inducing an inflammatory state can initiate a major depressive episode.
5. Stress is a common trigger for major depression and can also increase inflammation.

Increased rates of depression in people with inflammatory conditions

While association does not confirm causation, rates of depression are increased in people with inflammatory-related diseases. Autoimmune diseases such as diabetes (Andreoulakis et al., 2012), inflammatory bowel disease (Mikocka-Walus et al., 2007), multiple sclerosis (Alschuler et al., 2013), psoriasis (Biljan et al., 2009; Schmitt and Ford, 2010), rheumatoid arthritis (Matcham et al., 2013), and systemic lupus erythematosus (Palagini et al., 2013) are all associated with an increased prevalence of depression. Cardiovascular diseases (Fenton and

Stover, 2006), metabolic syndrome (Butnoriene et al., 2014), obesity (Lopresti and Drummond, 2013), and asthma (Ahmedani et al., 2013) are also accompanied by higher rates of depression. While the relationship may be accounted for by psychological, psychosocial and physical influences, inflammatory-related processes which affect neuroimmunological and neuroendocrine pathways are also likely to be important.

Increased inflammatory and immune response in major depression

Major depression is accompanied by an activated immuno-inflammatory response, including signs of low-grade inflammation and increased CMI. From several meta-analyses, it has been confirmed that major depression in community and clinic-based samples is associated with elevated levels of C-reactive protein (CRP) (Howren et al., 2009; Valkanova et al., 2013), tumour necrosis factor alpha (TNFα) (Dowlati et al., 2010; Liu et al., 2012), interleukin (IL)-6 (Dowlati et al., 2010; Hiles et al., 2012; Howren et al., 2009; Liu et al., 2012), IL-1 (Howren et al., 2009) and IL-2 receptor (sIL-2R) (Liu et al., 2012).

Cytokines such as interferon-γ (IFN-γ), IL-1β and TNFα can induce the enzyme indoleamine-2,3-dioxygenase (IDO). IDO is involved in the catabolism of tryptophan into TRYCATs (tryptophan catabolites along the IDO pathway) such as kynurenine (KYN), kynurenic acid (KYNA), and quinolinic acid (QUIN). These catabolites have neuroprotective (e.g., KYNA) and neurotoxic properties (e.g., QUIN). Although evidence is mixed, in general major depression is associated with increased IDO activity and lowered KNYA (Myint, 2012; Myint and Kim, 2013). From the evidence to date, it seems that increased IDO activity is prevalent in people with somatisation (Maes et al., 2011a; Maes and Rief, 2012) and in depressed patients with a history of suicidal attempts (Sublette et al., 2011).

Further support for an increased immune response in depression is provided by consistent discoveries of elevated immunoglobulin (Ig)M and IgA-mediated immune

responses against LPS from various Gram-negative bacteria (Maes et al., 2008; Maes et al., 2012). This is suggestive of the presence of increased gut permeability (leaky gut) and bacterial translocation.

Inducing an inflammatory state triggers depression

Stimulation of an inflammatory response using vaccinations, endotoxins, LPS and interferon can induce depressive symptoms (Rosenblat et al., 2014). For example, IFN-α, which is commonly used for the treatment of hepatitis C, triggers the onset of depression in 25 to 80% of patients (Raison et al., 2009; Udina et al., 2012; Wichers et al., 2005). The administration of LPS can also influence mood and cognitive ability (Grigoleit et al., 2011). While these studies suggest that inflammation has a causative role in depression, these findings need to be tempered by the fact that INF-α therapy involves the administration of supraphysiologic doses that are far higher than levels seen in depression. Nevertheless, low-dose LPS or typhoid vaccination are more modest but also yield depressive and anxiety symptoms (Raison and Miller, 2011).

Stress triggers depression and induces inflammation

Acute and chronic stressful events and traumatic experiences are common triggers for a major depressive episode (Muscatell et al., 2009; Tennant, 2002). Acute psychological stress is accompanied by an acute inflammatory response such as elevations in IL-6, IL-1β, TNFα, and CRP (Steptoe et al., 2007). Threats to social status (Kemeny, 2009), early life stress (Raposa et al., 2014) and bereavement (Cohen et al., 2013) are risk factors for the onset of depression and are also associated with increased inflammation.

Anti-inflammatory treatments have anti-depressant effects

Several medications with anti-inflammatory mechanisms have antidepressant effects. For example, used in conjunction with antidepressant medications, the COX-2 inhibitor celecoxib

can enhance treatment response and remission rates (Abbasi et al., 2012; Fond et al., 2014). Omega-3 fatty acids, which have anti-inflammatory properties, have moderate efficacy for the treatment of depressive symptoms in people with major depression (Grosso et al., 2014). Acetyl-salicylic acid (Berk et al., 2013) and the tetracycline antibiotic minocycline also have demonstrated antidepressant effects (Dean et al., 2012; Soczynska et al., 2012). In addition to these findings, in several reviews it has also been confirmed that antidepressants have anti-inflammatory properties (Hannestad et al., 2011; Leonard, 2013; Walker, 2013).

While the reviewed studies support an association between depression and immuno-inflammatory pathways, this does not necessarily imply causation. It seems that the relationship is likely bi-directional. However, support for inflammation as a causative factor is provided by consistent signs of depression following the induction of inflammatory processes (e.g via IFN-α and LPS). Control for moderating variables associated with inflammation and depression such as age, medical disease, smoking status and BMI, diminish the strength of the relationship but do not eliminate it.

Immuno-inflammatory states and their relationship with depressogenic pathways

The depressogenic mechanisms associated with dysregulated immune-inflammation have been comprehensively covered in several reviews. Immuno-inflammatory processes can influence neurotransmitter activity, contribute to HPA dysregulation, increase O&NS, impair mitochondrial function, and influence neuroprogression (Haroon et al., 2012; Leonard and Maes, 2012; Miller and Raison, 2008; Raison et al., 2006). A selection of inflammatory-induced mechanisms associated with these pathways is outlined below:

- *Neurotransmitter activity:* Immuno-inflammatory processes can influence neurotransmitter metabolism through several mechanisms. For instance, cytokines such as IFN-γ, IL-1β and TNFα can activate IDO leading to the breakdown of tryptophan, reducing subsequent

serotonin availability and increasing the production of TRYCATs (Myint, 2014). Chronic inflammation also lowers concentrations of tetrahydrobiopterin (BH4), an enzyme cofactor involved in the production of dopamine, nitric oxide (NO), noradrenaline and serotonin (Sperner-Unterweger et al., 2014). Cytokines and their signalling pathways can also influence the reuptake of monoamines and induce changes in serotonin receptors (Leonard and Maes, 2012; Miller et al., 2009).

- *HPA activity:* Cytokines disrupt HPA axis activity by up-regulating CRH, ACTH and cortisol release (Zunszain et al., 2011). Inflammatory cytokines can also disrupt GR function, contributing to glucocorticoid resistance (Pace and Miller, 2009).
- *Oxidative and nitrosative stress:* While O&NS can induce an inflammatory and immune response, the reverse is also true. For example, pro-inflammatory cytokines such as TNFα and IL-1β can stimulate the production of reactive oxygen species (ROS) (Barth et al., 2009; Floyd et al., 1999). Neopterin, a marker of Th1-type immune response, also activates inducible nitric oxide synthase and NO production, and increases levels of hydrogen peroxide (Razumovitch et al., 2004; Schobersberger et al., 1995). IDO activation induced by an immune reaction lowers concentrations of tryptophan and serotonin, which are both strong antioxidants, and increase oxidative stress-producing TRYCATs such as 3-hydroxykynurenine, 3-hydroxyanthranilic acid and quinolinic acid (Maes et al., 2011b).
- *Mitochondrial activity:* Pro-inflammatory cytokines can directly influence mitochondrial activity which, in turn, exacerbates inflammatory responses. Adipocytes treated with IL-6 had decreased mitochondrial membrane potential, decreased cellular ATP production, and increased intracellular ROS levels (Ji et al., 2011). The TRYCATs L-kynurenine, 3-hydroxykynurenine, anthranilic acid and 3-hydroxyanthranilic acid also disturb respiratory parameters of mitochondria (Baran et al., 2003).

- *Neuroprogression:* Increased levels of pro-inflammatory cytokines and CMI-related cytokines may contribute to neuroprogression through several mechanisms (Moylan et al., 2013). For instance, the stimulation of IDO produces several TRYCATs that can be neurotoxic to the central nervous system (CNS) (Myint and Kim, 2013); IFN-γ sensitises cortical and cerebellar neurons to neurotoxic peptides, and increases neuronal death (Bate et al., 2006; Lambertsen et al., 2004); and IFN-α decreases systemic BDNF levels (Kenis et al., 2011; Lotrich et al., 2013).

HPA dysregulation

A review of research on HPA axis dysregulation in major depression is covered in published papers in Chapters 3 and 4 (Lopresti et al., 2012; Lopresti et al., 2013), and therefore will not be repeated here. However, the influence of HPA activity on other dysregulated biological pathways is detailed below.

HPA activity and its relationship with depressogenic pathways

The importance of HPA activity in major depression is highlighted by its bi-directional relationship with several depressogenic biological pathways. In relation to inflammatory processes, pro-inflammatory cytokines have a significant influence on the development of glucocorticoid resistance and can contribute to increased cortisol secretion (Silverman and Sternberg, 2012). Sustained or severe stress can also promote the inflammatory response via pathways associated with the sympathetic and parasympathetic nervous systems (Turnbull and Rivier, 1999; Zunszain et al., 2011). HPA activity can also influence the immune response via its effect on the production of TRYCATs. Along with the enzyme IDO, tryptophan-2,3-dioxygenase (TDO), which is induced by cortisol, is also involved in the metabolism of tryptophan into TRYCATs (Altman and Greengard, 1966). Psychosocial stress can also increase free radical production and consequent oxidative stress; and sustained oxidative

stress via its damaging effects on brain centres, such as the hippocampus and hypothalamus, can impair HPA activity (Colaianna et al., 2013; Kobayashi et al., 2009). Severe or chronic exposure to stress, and consequent exposure to high cortisol levels during both early life and adulthood, can cause cell death, neuronal atrophy, and can affect hippocampal neurogenesis and plasticity (McEwen and Gianaros, 2011).

Oxidative and nitrosative stress

Oxidative and nitrosative stress (O&NS) and its relationship with major depression is summarised in published papers in Chapters 3 and 4 (Lopresti et al., 2012; Lopresti et al., 2013), and therefore will not be covered here.

O&NS and its relationship with depressogenic pathways

O&NS can contribute to the aetiology of depression via multiple depressogenic pathways. O&NS can influence serotonin activity by altering serotonin receptor sensitivity and receptor binding, and can damage intracellular signalling (Karolewicz et al., 2001; Zhang et al., 2010). It can elevate the production of inflammatory mediators such as pro-inflammatory cytokines and chemokines by increasing nuclear factor-κB, activator protein-1 and mitogen-activated protein kinases (Moylan et al., 2014). O&NS can also initiate autoimmune responses due to its deleterious effects on cellular proteins, lipids, and DNA. By changing the function and chemical structure of membrane fatty acids and functional proteins, modified immunogenic epitopes or neo-epitopes are formed, mounting an autoimmune response (Maes et al., 2011c). O&NS can also affect HPA axis activity. For example, elevation of NADPH oxidase in the hypothalamus altered HPA-axis activity (Colaianna et al., 2013), and oxidative stress in the form of hyperoxia, thiobarbituric acid reactive substances, conjugated diene and lipid hydroperoxides, markedly increased HPA axis activity and reduced glucocorticoid receptor concentrations. These effects were ameliorated by vitamin E supplementation (Kobayashi et

al., 2009). O&NS processes, including lowered antioxidant defences, are also a major cause of mitochondrial dysfunction (Gardner and Boles, 2011). The effects of O&NS on neuroprogression occur via most of the aforementioned pathways and through a complex series of events associated with excitotoxicity, calcium overload, and reduced neurotrophic factors (Kaur et al., 2005; Moylan et al., 2013; Numakawa et al., 2011).

Mitochondrial dysfunction

Published papers included in Chapters 3 and 4 (Lopresti et al., 2012; Lopresti et al., 2013) contain summaries of mitochondrial dysfunction in major depression and therefore will not be repeated here.

Mitochondrial activity and its relationship with depressogenic pathways

Mitochondrial dysfunction has a role in several depressogenic biological pathways. A deficiency in ATP production can contribute to fatigue and somatic symptoms associated with depression (Leonard and Maes, 2012). Mitochondria are very susceptible to damage by O&NS and, in turn, are major sources of ROS and reactive nitrogen species (RNS), further fuelling the O&NS process. ROS and RNS derived from mitochondria can also act as signal-transducing molecules that provoke an up-regulation of pro-inflammatory cytokines (Naik and Dixit, 2011). Mitochondria can also affect neuroprogressive pathways via their effect on cell death and subsequent neurodegeneration. For example, mitochondrial dysfunction impairs neural progenitor cell function (Kirby et al., 2009) and impairs neurogenesis-dependent hippocampal plasticity (Steib et al., 2014). All of these processes interact with mitochondrial activity, leading to a further cascade of mitochondrial abnormalities (Gardner and Boles, 2011; Moylan et al., 2013).

Neuroprogression

A review of research on neuroprogression in major depression is detailed in published papers attached in Chapters 3 and 4 (Lopresti et al., 2012; Lopresti et al., 2013).

Neuroprogression and its relationship with depressogenic pathways

Several pathways are posited to influence neuroprogression in major depression. Increased pro-inflammatory cytokines and immune responses; neurotoxic TRYCATs; elevated O&NS and lowered antioxidant defences; reduced serotonin metabolism; omega-3 essential fatty acid deficiency; mitochondrial dysfunction; chronic stress; and HPA dysregulation are all believed to be important pathways to neuroprogression (Haroon et al., 2012; Leonard and Maes, 2012; Moylan et al., 2013). Reduced neurotrophic factors such as BDNF also contribute to further cascading problems, as these factors are involved in serotonin metabolism (Homberg et al., 2014), HPA axis activity (Nowacka and Obuchowicz, 2013), mitochondrial activity (Markham et al., 2014; Nowacka and Obuchowicz, 2013), inflammatory responses (Audet and Anisman, 2013; Takeda et al., 2013), and O&NS (Boyadjieva and Sarkar, 2013; Numakawa et al., 2011).

Summary

As detailed in this chapter, several dysregulated biological pathways are associated with major depressive disorder. These pathways are strongly interconnected, having a multi-directional relationship. This can lead to a negative biological spiral, contributing to further dysregulation over time, and possible worsening of depressive symptoms. Although the original source of these disturbances is difficult to determine and may be unique to an individual, an understanding of the relationship between these pathways contributes to a greater understanding of the biological complexities associated with major depression.

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Chapter 3:
Lifestyle influences on biological mechanisms associated with major depression

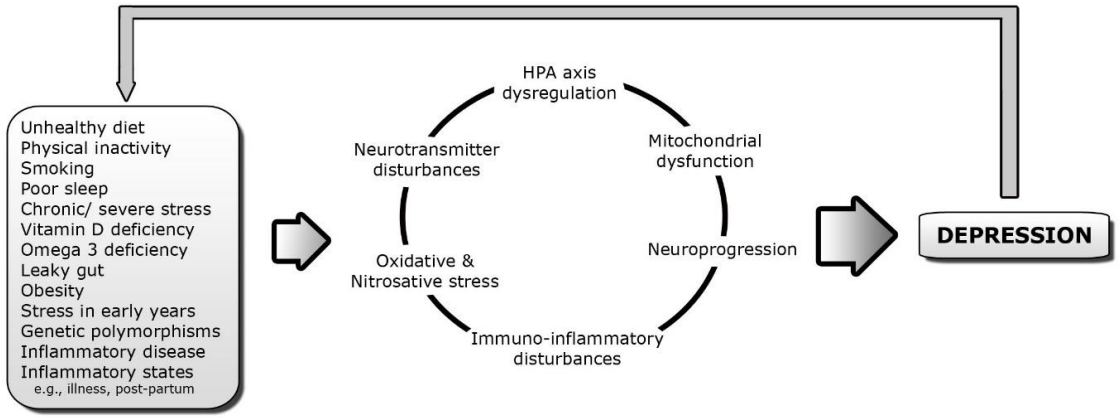

Figure 2. *Factors influencing biological pathways associated with depression*. The depressogenic biological pathways associated with major depression (centre of figure) are influenced by several past and current lifestyle, psychological, and biological factors (left of figure). These factors may affect one or several biological pathways, leading to further dysregulation. A bi-directional relationship exists between depression and these etiological factors (represented by the top arrow), as suffering from depression can also contribute to depressogenic lifestyle choices. A feed-forward process ensues, leading to a further exacerbation of depressive symptoms.

The depressogenic mechanisms associated with major depression reviewed in Chapter 2 are influenced by an array of biological, psychological, lifestyle and environmental factors (Figure 2). In a recent paper by Berk *et al.* (2013), the influence of psychosocial stressors, poor diet, physical inactivity, obesity, smoking, altered gut permeability, atopic disease, dental health, sleep and vitamin D deficiency on inflammatory processes associated with depression was reviewed. The postpartum period, other inflammatory disorders (e.g., cardiovascular disorder, rheumatoid arthritis, systemic lupus erythematosus, diabetes, and metabolic

syndrome) and several biological vulnerability factors also increase the propensity to develop depression, including a leaky gut with increased LPS translocation through the gut wall, and a lowered omega-3 essential fatty acid (EFA) status (Maes et al., 2009c).

A selection of important lifestyle-related factors (stress and trauma, omega-3 deficiency, vitamin D deficiency and smoking) associated with major depression is reviewed in the following sections with an examination of their influence on depressogenic biological pathways. Further lifestyle and physical influences such as diet, exercise, sleep and obesity are also reviewed in the attached published articles.

Stress and trauma

Psychosocial stressors, including acute psychological trauma, moderate chronic stressors, and early exposure to childhood trauma strongly increase the risk for major depression. In the 6 months prior to their worst depressive episode, people with major depression reported increased exposure to several significant stressors, including serious illness, injury or an assault; death of a spouse or first-degree relative; death of a close family friend or other relative; separation due to marital difficulties or break up of a steady relationship; a serious problem with a close friend, neighbour or relative; job loss; and major financial crisis (Hosang et al., 2012). These stressors can impact on cognitive and emotional resiliency and also influence several depressogenic biological pathways.

Stress and the immuno-inflammatory response

There is substantial evidence through animal models comprising chronic mild stress and learned helplessness that stress increases systemic and CNS levels of inflammatory markers, such as IL-1β, TNFα, IL-6, nuclear factor κB, COX-2, and expression of Toll-like receptors (Kubera et al., 2011). Similar findings have been observed in human-based studies. In a recent systematic review, it was confirmed that childhood trauma is associated with increased

baseline levels of inflammatory markers, most notably CRP, TNFα and IL-6 in adulthood (Coelho et al., 2014). In addition, lower socioeconomic status (SES) or lower early life social class is associated with higher levels of inflammatory signalling (Miller et al., 2009), which may be buffered by protective factors such as maternal warmth (Chen et al., 2011). In a meta-analysis it was also shown that acute psychological stress significantly augments levels of IL-6, IL-1β and CRP, but not TNFα (Steptoe et al., 2007). The effects of stress in people with major depression is of particular relevance as there is evidence that acute psychological stress is associated with an exacerbated inflammatory response in people with major depressive disorder (Miller et al., 2005; Pace et al., 2006).

Stress and HPA activity

Childhood trauma is consistently associated with dysregulated HPA activity, although the direction of activity is variable, with findings of both increased and decreased HPA activity. HPA axis functioning as measured by the cortisol awakening response was significantly increased in depressed patients with a history of childhood neglect compared to those without (Peng et al., 2014). In a non-clinical sample of women with minimal or no current psychopathology, a prior history of physical abuse was associated with a blunted cortisol response to a psychosocial stress task (Carpenter et al., 2011). However, postpartum women who reported experiencing adverse early life experiences exhibited a tendency toward higher levels of awakening cortisol compared to women with no adverse history (Gonzalez et al., 2009). In adults without diagnosable psychopathology, childhood maltreatment was associated with a diminished HPA axis response to a psychosocial stressor (Carpenter et al., 2007). It is argued that childhood trauma may influence GR sensitivity by down-regulating glucocorticoid expression (McGowan et al., 2009).

Stress and oxidative and nitrosative stress

Schiavone *et al.* (2012) reviewed animal and human based studies examining the influence of severe life stress on oxidative stress. Animal models of severe life stress comprised sleep deprivation, maternal separation and social isolation in rodents, and the establishment of a dominance hierarchy in non-human primates. Exposure to these differing forms of severe life stress was associated with decreased antioxidant enzymes such as glutathione peroxidase and superoxide dismutase. Rats exposed to social isolation also experienced increases in NADPH oxidase (NOX2) enzyme activity and increased markers of oxidative stress (Schiavone et al., 2009). In humans, severe life stress caused by traumatic events such as child abuse, war, and divorce, is accompanied by increased oxidative stress in the CNS (Schiavone et al., 2012). Increased levels of nitric oxide, ROS-mediated brain changes and elevations in 8-hydroxy-2-deoxyguanosine have been reported in soldiers exposed to war (Borovac Stefanovic et al., 2014; Pall, 2001).

Stress and neuroprogression

While mild, acute stress can enhance learning and memory and facilitate brain plasticity, chronic or severe stress, as well as exposure to high doses of glucocorticoids, can be harmful to the CNS leading to several structural changes such as neuronal atrophy in the hippocampus and prefrontal cortex (Sapolsky, 2003). In animal studies it has been shown that exposure to repeated or chronic stress causes plastic remodelling of hippocampal circuitry, such as the shortening of dendrites, loss of dendritic spine synapses, and suppression of neurogenesis (McEwen and Gianaros, 2011). Differences in the corpus callosum identified by structural magnetic resonance imaging (MRI) have now been reliably reported in children who have experienced abuse, while differences in the hippocampus have been found in adults with a childhood history of maltreatment. In addition, there is preliminary evidence of amygdala

hyperactivity and atypical activation in the frontal regions of adults who have experienced childhood maltreatment (McCrory et al., 2011). Low SES, which is associated with increased stress, also correlates with smaller hippocampal volumes (Cavanagh et al., 2013; Raizada and Kishiyama, 2010), and high levels of chronic perceived stress over a 20-year period in postmenopausal women has been associated with reduced gray matter volume in the hippocampus and in a region of the lateral prefrontal cortex (Gianaros et al., 2007).

Investigations into the effects of stress on neurotrophic factors have confirmed that chronic and severe stress has a detrimental effect on BDNF. The expression of BDNF is regularly reduced in experimental animals exposed to adverse experiences at early stages of life or during adulthood (Calabrese et al., 2009), and exposure both to early and later life trauma elicits significant down-regulation in BDNF mRNA and protein levels in the hippocampus CA1 subregion (Bazak et al., 2009).

Stress and monoaminergic activity

In animal models, stress alters serotonergic activity. For example, early life stress comprising prolonged maternal separation disturbed the serotonergic system by altering adult brain serotonergic transporter function and 5-HT_{1A} receptor and SERT mRNA expression (Bravo et al., 2014; Ohta et al., 2014; Vicentic et al., 2006). The serotonergic system is also altered by acute physical stress (Choi et al., 2014), and exposure to excessive prenatal stress may induce a vulnerability to stress and disrupt the development of serotoninergic neurons (Miyagawa et al., 2014).

Stress also influences dopaminergic activity. For example, maternal separation in rats altered dopamine transporter function (Womersley et al., 2011) and tyrosine hydroxylase-immunoreactive dopaminergic neurons in the rat midbrain (Chocyk et al., 2011). Acute psychological stress comprising exposure to traumatic imagery in people with war-related,

chronic post-traumatic stress disorder (PTSD) lowered cerebrospinal fluid (CSF) levels of the dopamine metabolite homovanillic acid compared to exposure to neutral imagery (Geracioti et al., 2013).

These reviewed studies confirm that acute and chronic stress can influence several depressogenic biological pathways. Although the influence of stress on each pathway has been discussed separately, they are strongly inter-connected. Other variables including age, gender, SES, ethnicity, body-mass index, cardiorespiratory fitness, sleep quality and quantity, caffeine consumption, smoking and alcohol consumption also likely influence these mechanistic pathways (O'Connor et al., 2009).

Omega-3 deficiency

A relationship between omega-3 essential fatty acids (EFA) and depression is supported by several lines of evidence. For example, omega-3 levels are often lower in depressed people compared to healthy controls; omega-3 status is often associated with depressive symptoms; and supplementation with omega-3 EFAs are regularly associated with improvements in depressive symptoms.

Omega-3 status and depression

In a meta-analysis of 14 studies, the levels of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and total omega-3 EFA were significantly lower in depressed patients compared to control subjects. However, there was no significant difference in arachidonic acid or total omega-6 levels between the two groups (Lin et al., 2010).

After adjusting for body mass index, serum total cholesterol level and SES, the risk of developing depression increased up to 2.6-fold among females who rarely ate fish compared with regular fish eaters (Timonen et al., 2004). In a longitudinal population-based study on 3317 African-American and Caucasian men and women, Colangelo *et al*. (2009) examined the

association between fish consumption and dietary intake of EPA and DHA with depressive symptoms. In the entire cohort, the highest quintiles of EPA, DHA, and EPA + DHA intake were associated with a lower risk of subsequent depressive symptoms with more pronounced associations observed in women. However, not all findings from cohort studies support a relationship between omega-3 consumption and depression. For example, in a 10-year prospective study on 54,632 women aged 50-77 years, the intake of omega-3 EFA from fish was not associated with subsequent depression risk, although α-linolenic acid intake was inversely associated with risk of depression (Lucas et al., 2011). Little evidence from a large prospective cohort was also found between intake of fish and post-partum depression (Strom et al., 2009).

While omega-3 intake can provide an indicator of EFA status, blood concentrations of EFA can provide another marker. In several studies it has been confirmed that EFA concentrations in blood are lower in depressed populations compared to controls. For example, lower concentrations of total omega-3 EFA and DHA in red blood cells (Peet et al., 1998) and omega-3 EFA in serum phospholipids (Maes et al., 1999) were found in depressed patients compared to healthy controls. Low red blood cell concentrations of omega-3 during late pregnancy was also associated with higher depression scores three months postpartum (Markhus et al., 2013).

Supplementation with omega-3 PUFA is associated with improvements in depressive symptoms.

Interest in the antidepressant effects of omega-3 supplementation in people with major depression has been high. Consequently, several systematic reviews and meta-analyses have been published over the past decade. On the whole, it has been confirmed that omega-3 supplementation is beneficial for the alleviation of depressive symptoms (Appleton et al.,

2010; Kraguljac et al., 2009). In a recent meta-analysis comprising 11 studies on patients with a DSM-defined diagnosis of major depressive disorder, and 8 trials on patients with depressive symptomatology but no diagnosis of major depression, significant clinical benefit from omega-3 treatment compared to the placebo was confirmed. In trials on people with diagnosed major depression, preparations containing greater concentrations of EPA compared to DHA were associated with greater clinical efficacy (Grosso et al., 2014b). Similar findings have been obtained from other meta-analyses, demonstrating greater benefits from supplements with greater EPA concentrations (Martins, 2009; Sublette et al., 2011).

The relationship between omega-3 EFA and depression may be due to its influence on multiple antidepressant mechanisms of action. Omega-3 EFA influences several molecular pathways associated with inflammation. The anti-inflammatory actions of omega-3 EFA are thought to be mediated by the formation of their active metabolites (eicosanoids and other lipid mediators) as well as their regulation of the production of inflammatory mediators (e.g., adipocytokines, cytokines) and immune cell infiltration into adipose tissue (Grosso et al., 2014a). Omega-3 EFAs mediate these effects by modulating several pathways, such as those involving nuclear factor-κB, peroxisome proliferator-activated receptors and Toll-like receptors (Fan et al., 2013). Higher dietary omega-3 intake is also associated with lower levels of inflammatory and endothelial activation biomarkers in cardiovascular disease, renal disease, sepsis and acute pancreatitis (Rangel-Huerta et al., 2012). The anti-inflammatory effects of omega-3 EFAs are also related to their influence on resolvins, which are potent anti-inflammatory mediators that act as 'stop-signals' on the inflammatory response (Titos and Claria, 2013).

The beneficial effects of omega-3 on depression may also occur via its influence on HPA activity and cortisol regulation. For example, in a randomised, placebo-controlled trial on abstinent alcoholics, fish oil supplementation was associated with reduced basal cortisol levels

(Barbadoro et al., 2013). In people with recurrent depression, cortisol levels correlated negatively with blood DHA concentration (Mocking et al., 2013). Fish oil supplementation also significantly blunted plasma ACTH and cortisol levels in healthy volunteers following an endotoxin challenge comprising LPS (Michaeli et al., 2007). EPA alone or in combination with fluoxetine, as well as fluoxetine alone, decreased serum cortisol after 8 weeks of treatment in patients with major depressive disorder (Jazayeri et al., 2010). Finally, supplementation with omega-3 EFAs inhibited increases in plasma epinephrine and cortisol elicited by acute mental stress in healthy men (Delarue et al., 2003).

Omega-3 EFAs also have positive effects on neurogenesis in the hippocampus (Kang and Gleason, 2013; Kawakita et al., 2006). In animal models, exposure to omega-3 EFAs enhanced adult hippocampal neurogenesis, promoted synaptic plasticity and modulated synaptic protein expression (Crupi et al., 2013). In contrast, decreased DHA in the developing brain impairs neurogenesis, neurotransmitter metabolism, and alters learning in animals (Innis, 2008). In further animal studies it has been confirmed that omega-3 supplementation during the prenatal period increases concentrations of BDNF and nerve growth factor (Sable et al., 2013). Human-based studies are scarce, although in an open-label study on people with PTSD, fish oil supplementation was associated with increases in serum BDNF levels (Matsuoka et al., 2011). However, no effect on BDNF was found in depressed, diabetic patients supplemented with fish oil (Bot et al., 2011).

Vitamin D deficiency

Vitamin D, the 'sunshine vitamin', is well known for its role in regulating calcium and phosphate metabolism and for skeletal health. Because most cells and organs in the body have a vitamin D receptor, vitamin D also influences several biological pathways. Vitamin D deficiency has been linked to many chronic diseases including autoimmune diseases, some

cancers, cardiovascular disease, infectious disease, and type 2 diabetes (Glade, 2013; Wacker and Holick, 2013). Research over the past decade also confirms a relationship with depression.

In a systematic review and meta-analysis, Anglin *et al*. (2013) analysed one case–control study, ten cross-sectional studies and three cohort studies on depression and vitamin D deficiency (total of 31,424 participants). In the case-control study, vitamin D levels in women with depression were lower compared to healthy controls, represented by a standard mean difference of 0.60 (95% CI 0.23–0.97). In a meta-analysis on the ten cross-sectional studies, there was an increased but non-significant odds ratio of depression for the lowest compared to highest vitamin D categories (OR = 1.31, 95% CI 1.0-1.71). In the three identified cohort studies, there was a significantly increased hazard ratio of depression for the lowest versus highest vitamin D categories (HR = 2.21, 95% CI 1.40-3.49) (Anglin et al., 2013). In another meta-analysis, 11 cross-sectional studies (43,137 participants) and 5 cohort studies (12,648 participants) were identified for analysis. A 10 ng/ml increase in vitamin D level was associated with an 8% decrease in the incidence of depression in cohort studies and a 4% decrease in the risk of depression in cross-sectional studies (Ju et al., 2013).

Several recent meta-analyses have also now been published examining the effects of vitamin D supplementation on depressive symptoms. In a meta-analysis of six randomised controlled trials consisting of 1203 participants (5 studies involving adults at risk of depression, and one using depressed patients), there was no identified significant effect for vitamin D supplementation compared to placebo on post-intervention depression scores (Li et al., 2014). In another meta-analysis on seven randomised controlled trials (3,191 participants), vitamin D supplementation again had no overall effect on depressive symptoms, although a subgroup analysis showed that vitamin D supplementation in participants with clinically significant depressive symptoms or depressive disorder had a moderate, statistically significant effect (2 studies: standardised mean difference, -0.60; 95% CI, -1.19 to -0.01; p = .046)

(Shaffer et al., 2014). Finally, in a meta-analysis by Spedding (2014), studies without methodological flaws were analysed. Methodological flaws were defined as follows: studies where vitamin D supplementation was associated with reduced or no change in post-intervention vitamin D status; studies where the baseline vitamin D level was not measured in participants; and studies where the baseline vitamin D level indicated sufficiency at baseline. Using only studies with no methodological flaws, it was concluded that vitamin D supplementation (≥800 I.U. daily) was effective for the management of depression with the effect size comparable to that of anti-depressant medication.

While further research is required, from the bulk of the evidence to date, it seems that vitamin D has a role in major depression. This relationship likely results from the multiple biological actions of vitamin D. For example, vitamin D can regulate serotonin synthesis by activating the transcription of the serotonin-synthesising enzyme, tryptophan hydroxylase 2 (Patrick and Ames, 2014), and can influence dopamine production via its effect on the expression of the enzymes catechol-O-methyl transferase and tyrosine hydroxylase (Kesby et al., 2009; Partonen, 1998; Tekes et al., 2009). Vitamin D also influences the body's immune system by modulating the innate and adaptive immune systems, affecting the production of important endogenous antimicrobial peptides and regulating the inflammatory cascade (Arnson et al., 2007; Gunville et al., 2013). In a study by Arnoson *et al.* (2013), a course of treatment with vitamin D for 5 days attenuated the increase in circulating levels of inflammatory cytokines after an acute coronary event. Control patients had increased serum concentrations of cytokine and cellular adhesion molecules after 5 days (VCAM-1 levels, CRP, and IL-6), while the vitamin D-treated group had an attenuated elevation or a reduction in these parameters. Vitamin D can also affect HPA regulation through its influence on glucocorticoid action and glucocorticoid receptor sensitivity (Obradovic et al., 2006; Zhang et al., 2013). Finally, in animal studies, vitamin D depletion is also associated with altered

neurogenesis (Cui et al., 2007; Zhu et al., 2012). The neuroprotective effect of vitamin D is associated with its influence on neurotrophin production and release, neuromediator synthesis, intracellular calcium homeostasis, and prevention of oxidative damage to nervous tissue (Xu et al., 2006).

Smoking

In several population-based epidemiological studies, it has been confirmed that rates of cigarette smoking are significantly higher in depressed patients compared to non-depressed controls (Lasser et al., 2000; Lawrence et al., 2009). In the National Comorbidity Survey, approximately 59% of individuals with a life-time history of depression were current or past smokers, compared to less than 39% of those without a life-time history of depression (Lasser et al., 2000; Ziedonis et al., 2008).

The relationship between depression and smoking is likely bi-directional as findings in most studies have shown that depression increases the likelihood of smoking onset, and smoking increases the risk of later depression. For example, in adolescence, depression and anxiety predicted the initiation of experimental smoking (Patton et al., 1998), and in a sample of 15 to 54 year olds, having an unremitted, pre-existing psychiatric disorder was associated with an increased risk of *de novo* smoking and progression to nicotine dependence (Breslau et al., 2004). Smoking also appears to be associated with an increased risk for later development of mood disorders. Using a case-control and retrospective cohort study design, Pasco *et al.* (2008) demonstrated that smoking increased the risk of *de novo* major depressive disorder by 93%; and in a 13-year longitudinal study using a population-based sample of 13 to 27 year olds, nicotine-dependent young adults had an elevated risk for the development of anxiety, depression and parasuicide (Pedersen and von Soest, 2009). In addition to increased prevalence rates, people with current nicotine dependence also exhibit greater severity of

depressive symptoms and experience a slower recovery from depression compared to people without a history of nicotine dependence (Jamal et al., 2012; Leventhal et al., 2009).

The effects of smoking on neurobiological depressogenic pathways have been described in several reviews (Berk et al., 2013; Moylan et al., 2013b; Nunes et al., 2013; Vargas et al., 2013). Smoking influences monoaminergic activity, HPA axis regulation, immuno-inflammatory processes, O&NS and mitochondrial activity. In particular, smoking has been associated with increased levels of acute phase proteins, including CRP, and pro-inflammatory cytokines, such as IL-1β, IL-6 and TNFα (Yanbaeva et al., 2007). It also seems that the effects of smoking and depression are additive as inflammatory responses are enhanced in depressed smokers compared to non-depressed smokers (Nunes et al., 2012).

The free radicals contained in cigarette smoke also lead to oxidative damage to cellular tissues, including those in the CNS. In several animal studies cigarette smoke increased markers of oxidative stress and decreased levels of antioxidants and antioxidant enzymes (Frost-Pineda et al., 2011; Stangherlin et al., 2009; Tuon et al., 2010). Cigarette smoking also influences neurotransmitter activity. For example, in a study by Malone, *et al.* (2003), an inverse relationship was observed between the amount of cigarette smoking and serotonin function in psychiatric patients. In an animal model, cigarette smoking influenced dopamine activity by increasing dopamine transporter expression (Li et al., 2004).

Diet, Sleep, Exercise and Obesity

In the following two published papers, the relationship between depression and diet, exercise, sleep and obesity are reviewed. Their potential impact on the depressogenic biological pathways is also examined.

A review of lifestyle factors that contribute to important pathways associated with major depression: Diet, sleep and exercise

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Abstract

Research on major depression has confirmed that it is caused by an array of biopsychosocial and lifestyle factors. Diet, exercise and sleep are three such influences that play a significant mediating role in the development, progression and treatment of this condition. This review summarises animal and human-based studies on the relationship between these three lifestyle factors and major depressive disorder, and their influence on dysregulated pathways associated with depression, namely neurotransmitter processes, immuno-inflammatory pathways, hypothalamic-pituitary-adrenal (HPA) axis disturbances, oxidative stress and antioxidant defence systems, neuroprogression, and mitochondrial disturbances. Increased attention in future clinical studies on the influence of diet, sleep and exercise on major depressive disorder and investigations of their effect on physiological processes will help to expand our understanding and treatment of major depressive disorder. Mental health interventions, taking into account the bidirectional relationship between these lifestyle factors and major depression are also likely to enhance the efficacy of interventions associated with this disorder.

Introduction

Technological advances have changed how we communicate, the activities we engage in, our occupational and recreational pursuits, and even the foods that we eat. While sport and leisure activity levels have remained stable or increased slightly over time, physical activity associated with work, home, and transportation has declined significantly (Brownson et al., 2005; Juneau and Potvin, 2010). In the United States it was estimated that over the past 50 years occupation-related energy expenditure decreased by more than 100 calories/day (Church et al., 2011). Driving to work increased from 67% of the working north American population in 1960 to 88% in 2000 (Brownson et al., 2005) and, in U.S. schoolchildren, walking or riding bikes to school decreased from 40% in 1969 to 13% in 2001 (McDonald, 2007). Dietary changes are also significant as worldwide sugar consumption has increased by 74-kcal/day per person from 1962 to 2000. Of this increase, 80% was derived from sugared beverages with additional contributions from restaurant and fast food sources (Popkin and Nielsen, 2003). Alarmingly, sugar consumption has increased most in children aged 6-11 years with an approximate 20% increase from 1988 to 2004 (Wang et al., 2008).

These and other changes of modernity over the past few decades have coincided with a reported increase in the prevalence of many psychiatric problems, including major depression. Between 1991-92 to 2001-2, one-year prevalence rates of major depression increased from 3.33% to 7.06% in a community population of American adults (Compton et al., 2006). Increases have also been observed in Australian communities with prevalence rates rising from 6.8% to 10.3% between 1998 and 2008 (Goldney et al., 2010). While these increased rates of depression may be due, in part, to improvements in diagnostic recognition, changes in diagnostic criteria and increased community acceptance of this condition, contemporary lifestyles might also explain why depression is on the rise. However, underlying mechanisms

are not well understood. This review provides a summary of three major lifestyle mediators - diet, exercise and sleep - associated with major depression and their impact on a range of relevant biological and physiological pathways.

Methods

Search strategy

The PubMed, Google Scholar, and PsycInfo databases were searched from all years of record until August 2012. Most references were obtained from combinations of the following key terms: “depression”, “diet”, “nutrients”, “sleep”, “exercise”, “inflammation”, “oxidative stress”, “mitochondria”, “neurogenesis”, “BDNF”, “HPA”, “cortisol”, “serotonin” and “monoamines”. The reference lists of relevant papers were also examined to locate additional studies that were not identified by the database searches.

Eligibility criteria

Studies were included in this review if they were published in English, comprised animal or human investigations and examined areas of exercise, sleep or diet and their impact either on inflammation, hypothalamic–pituitary–adrenal (HPA) axis, neurotransmitters, neuroprogression and oxidative/nitrosative stress.

Dysregulated pathways in major depression

Major depression has a multifactorial etiology arising from environmental, psychological, genetic and biological factors. As outlined in figure 1, research over the past decade has clarified that depression is associated with neurotransmitter imbalances, HPA disturbances, dysregulated inflammatory pathways, increased oxidative and nitrosative damage, neuroprogression, and mitochondrial disturbances (Leonard and Maes, 2012; Lopresti et al.,

2012; Maes et al., 2009c; Manji et al., 2001; Raison and Miller, 2011). While these disturbances will each be discussed briefly they are not mutually exclusive.

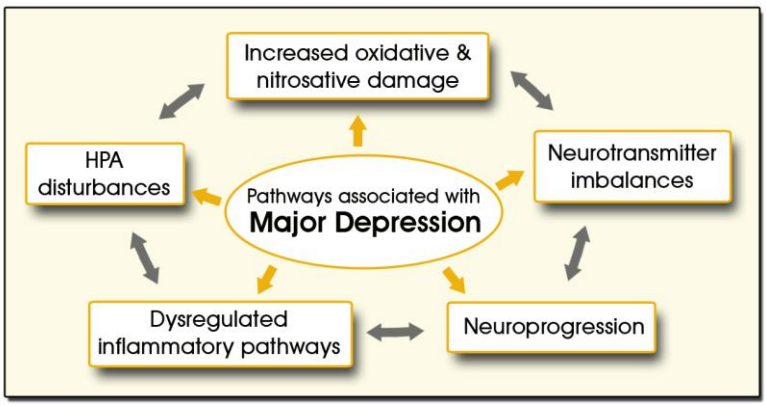

Figure 1. Multiple pathways associated with major depression

Neurotransmitter imbalances

Imbalances in the production and transmission of neurotransmitters such as serotonin, dopamine, noradrenaline and glutamate are commonly observed in the central nervous system in major depression (Maletic et al., 2007). Deficiencies in serotonin availability, the most extensively studied neurotransmitter in depression, is supported by studies using tryptophan depletion models (which reduces central serotonin synthesis) (Hood et al., 2005; Toker et al., 2010) and findings of serotonin receptor abnormalities in depressed patients (Carr and Lucki, 2011). Depression is also associated with an increased availability of monoamine oxidase, an enzyme that metabolises serotonin and other monoamines in the brain (Meyer et al., 2006), and abnormalities in the expression of the enzyme tryptophan hydroxylase, which is involved in serotonin synthesis (Matthes et al., 2010). However, the strongest evidence of neurotransmitter imbalances in depression comes from the popular use and efficacy of pharmaceutical antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), which are thought to alleviate depression by increasing the availability of monoamines such as

serotonin, noradrenaline (i.e., norepinephrine) and, possibly, dopamine (Connolly and Thase, 2012).

HPA disturbances

Dysfunction in the HPA axis is common in patients with major depression (Pariante and Lightman, 2008). This is characterised by heightened cortisol secretion in patients presenting with melancholic depression, and reduced levels in atypical depression (Gold and Chrousos, 2002). Depression is also associated with hypersecretion of corticotropin-releasing hormone (CRH) and impairment in responsiveness to glucocorticoids (Pariante and Lightman, 2008). An increased size and activity of the pituitary and adrenal glands are also found in major depression (Nemeroff et al., 1992). Successful treatment with antidepressants is associated with a normalisation of HPA axis activity and restoration in glucocorticoid receptor function (Anacker et al., 2011a; Anacker et al., 2011b).

Oxidative & nitrosative stress

Decreased antioxidant status and elevated oxidative and nitrosative stress are found in patients with major depression (Maes et al., 2011a). This is evidenced by reduced plasma concentrations of important antioxidants such as vitamin C (Khanzode et al., 2003), vitamin E (Maes et al., 2000; Owen et al., 2005), and coenzyme Q_{10} (Maes et al., 2009b), and by reduced antioxidant enzyme activity such as glutathione peroxidase (Maes et al., 2011e). These deficiencies in antioxidant defences impair protection against reactive oxygen species (ROS), leading to damage to fatty acids, proteins and DNA (Maes et al., 2011a).

Depression is also associated with increased levels of lipid peroxidation, comprising elevations in malondialdehyde (Ozcan et al., 2004; Sarandol et al., 2007; Wei et al., 2009), and increased oxidative damage to DNA, characterised by increased levels of 8-hydroxy-2-deoxyguanosine (Forlenza and Miller, 2006; Maes et al., 2009a). Depression is also associated

with increased plasma levels of peroxides and xanthine oxidase (Herken et al., 2007; Maes et al., 2010). The efficacy of antioxidant therapies for depression is unknown, although N-acetylcysteine, a powerful antioxidant, was found to be useful for depressive episodes in bipolar disorder (Berk et al., 2008; Magalhaes et al., 2011) and zinc, which serves as a strong antioxidant, also has antidepressant activity (Szewczyk et al., 2011).

Neuroprogression

Neurogenesis and neuronal plasticity are compromised in major depression, with subsequent neurodegeneration (Lee and Kim, 2010). This results in stress-induced alterations to the number and shape of neurons and glia in brain regions of depressed patients (Duman, 2009) and decreased proliferation of neural stem cells (Eyre and Baune, 2012).

Brain-derived neurotrophic factor (BDNF) is the most abundant and widely distributed neurotrophin in the central nervous system, involved in neuronal survival, growth and proliferation (Martinowich and Lu, 2008). BDNF levels are low in people with major depression (Duman, 2009; Lee and Kim, 2010). However, BDNF levels increase with chronic administration of several classes of antidepressants, including monoamine oxidase inhibitors, SSRIs, tricyclic agents, and SNRIs (Duman and Monteggia, 2006; Sen et al., 2008). Early life and chronic stress, which is often typical in patients with major depression, also has detrimental effects on BDNF (Martinowich et al., 2007; Nagahara and Tuszynski, 2011).

Mitochondrial disturbances

Mitochondria are intracellular organelles that generate most of the cell's supply of adenosine triphosphate (ATP) and are also involved in a range of other processes such as signalling, cellular differentiation, cell death, and the control of the cell cycle and cell growth (McBride et al., 2006). High concentrations of mitochondria are found in the brain which increases its vulnerability to reductions in aerobic metabolism (Pieczenik and Neustadt, 2007).

Depression is associated with mitochondrial dysfunction or disease with evidence of deletions of mitochondrial DNA (Gardner and Boles, 2008a; Shao et al., 2008), and lower activities of respiratory chain enzymes and ATP production (Gardner et al., 2003). Depressed patients presenting with somatic complaints also have low ATP production rates in biopsied muscles (Gardner and Boles, 2008a; Gardner and Boles, 2008b). In addition, rates of depression are increased in patients with mitochondrial disorders (Fattal et al., 2007; Koene et al., 2009).

Immuno-inflammation

Increased inflammation in major depression has been confirmed in three recent meta-analyses. Elevated levels of C-reactive protein (CRP), interleukin-1 (IL-1), and interleukin-6 (IL-6) were reported in a meta-analysis on depression in clinic and community samples (Howren et al., 2009), levels of tumour necrosis factor-α (TNF-α) and IL-6 were significantly higher in depressed patients than controls (Dowlati et al., 2010), and blood levels of soluble interleukin-2 receptors, TNF-α and IL-6 were higher in a meta-analysis on patients with major depressive disorder than controls (Liu et al., 2012b). Major depression is also characterised by a Th-1-like cell-mediated response, with evidence of increased production of interferon-γ (IFN-γ), increased IFN-γ/IL-4 ratios and increased neopterin levels (Maes et al., 1994; Myint et al., 2005). In addition, anti-depressant medications have anti-inflammatory effects (Hannestad et al., 2011).

An elevated immuno-inflammatory response in major depression is further supported by investigations into kynurenine pathway metabolites or TRYCATS (tryptophan catabolites along the IDO pathway) (Dantzer et al., 2011; Maes et al., 2011d). As shown in Figure 2, TRYCATS are produced by the breakdown of tryptophan, involving the enzyme indoleamine 2,3-dioxygenase (IDO). IDO is expressed in multiple cell types including macrophages, dendritic cells, astrocytes and microglia and is strongly activated by the pro-inflammatory

cytokine IFN-γ and to a lesser extent TNF-α, IL-1, and IL-6. These TRYCATS have both neurotoxic and neuroprotective qualities. Preliminary research has demonstrated a relationship between depression and low levels of the neuroprotective TRYCAT, kynurenic acid (KYNA) (Maes et al., 2011b; Myint et al., 2007; Wichers et al., 2005), and high levels of the excitotoxic TRYCAT, quinolinic acid (QUIN) (Raison et al., 2010a; Steiner et al., 2011). However, further research is warranted as Hughes et al., (2012) found no differences in IDO expression or plasma levels of TRYCATS between depressed patients and controls.

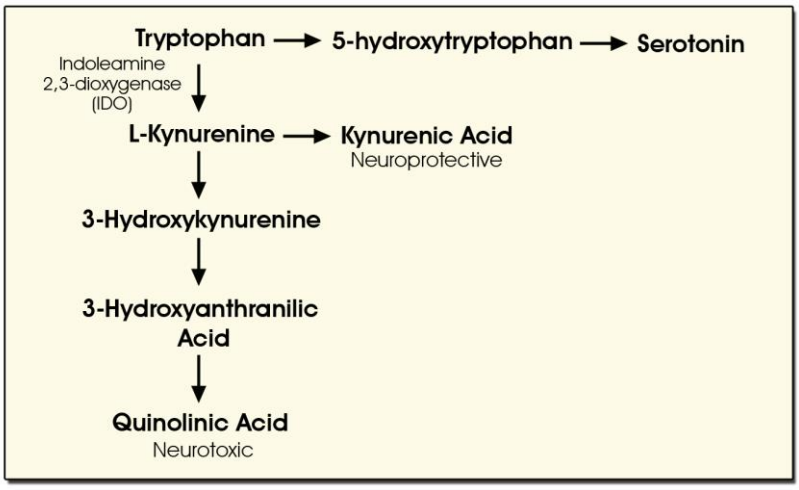

Figure 2. *Kynurenine pathway and its metabolites.* The kynurenine pathway starts with the degradation of tryptophan by the enzyme, indoleamine 2,3-dioxygenase (IDO) which is upregulated by pro-inflammatory cytokines (e.g. IFN-γ, TNF-α, IL-, IL-6). These TRYCATS (tryptophan catabolites along the IDO pathway) have neuroprotective and neurotoxic effects on the CNS and influence monoaminergic transmission.

Lifestyle factors associated with major depression

Dysregulation in the pathways reviewed above can be influenced by environmental, social, psychological, lifestyle, genetic and physiological factors (Hidaka, 2012; Leonard and Maes, 2012). Diet, sleep and exercise are three such influences that play an important role in the etiology, progression and treatment of depression. A bidirectional relationship likely exists between depression and these mediators.

The relationship between diet and depression

An association between diet and depression has now been confirmed in prospective and epidemiological studies. For example, in elderly men and women, the consumption of fish, vegetables, olive oil, and cereal correlated negatively with the severity of depressive symptoms (Mamplekou et al., 2010). The benefits from fish and olive oil intake remained significant even when adjusted for confounders such as age, sex, education status, BMI and physical activity status, as well as the presence of a number of medical conditions. In a prospective study, and after adjusting for sex, age, smoking status, BMI, physical activity levels and employment status, adherence to a Mediterranean diet comprising high levels of vegetables, fruit, nuts, cereal, legumes, and fish, a moderate alcohol intake, and a low consumption of meat or meat products and whole-fat dairy, was protective against the development of depression (Sanchez-Villegas et al., 2009). In a study by Jacka et al. (2010b), consuming a 'traditional' diet comprising vegetables, fruit, meat, fish, and whole grains was also associated with a 35% reduced risk of depression or dysthymia. Research into the diet of adolescents (Jacka et al., 2010a) and of low socio-economic, community dwelling, elderly people (German et al., 2011) has also provided evidence for an association between diet quality and depression. Depressive symptoms are also positively associated with the consumption of sweets (Jeffery et al., 2009). Similarly, high intake of fast food (hamburgers, sausages, pizza) and processed pastries (muffins, doughnuts, croissants) are associated with an increased risk of depression up to 6 years later (Sanchez-Villegas et al., 2012).

High-quality treatment studies investigating the impact of diet on depression are scarce, although in a randomised-controlled trial, meat-eating adults placed on a two-week vegetarian diet reported significantly greater improvements in mood compared to participants who continued to eat meat, fish or poultry (Beezhold and Johnston, 2012). In another

randomised-controlled trial, six days on a low protein diet significantly decreased depressive symptoms in type 2 diabetics (Ciarambino et al., 2011), and in a randomised study on overweight and obese individuals, those placed on an energy-restricted, low-fat diet for one year experienced greater improvements in mood compared to participants on an energy-restricted, low-carbohydrate diet (Brinkworth et al., 2009). These changes were independent of weight loss.

Polyunsaturated fatty acids (PUFAs) and particularly omega-3 essential fatty acids (ω-3 EFA) have received significant attention in relation to depression. In a meta-analysis of 14 studies comparing the levels of PUFAs between depressed patients and control subjects, the levels of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and total ω-3 EFA were significantly lower in depressed patients than controls (corresponding to effect sizes of -0.18, -0.35 and -0.51, respectively). There was no significant change in arachidonic acid (AA) or total ω-6 PUFAs (Lin et al., 2010). A meta-analysis of the effects of EPA supplementation in 15 clinical trials in depressed populations revealed beneficial effects from fish oil containing high levels of EPA (effect size = 0.53) (Sublette et al., 2011).

Other investigations on the relationship between nutrients and depression have demonstrated a role of folate (Farah, 2009; Gilbody et al., 2007; Morris et al., 2008), tryptophan (Cowen et al., 1989; DeMyer et al., 1981; Maes et al., 1987), zinc (Cope and Levenson, 2010; Lai et al., 2012; Szewczyk et al., 2011), iron (Maes et al., 1996; Stewart and Hirani, 2012; Vahdat Shariatpanaahi et al., 2007; Yi et al., 2011), CoQ10 (Maes et al., 2009b), vitamin B6 (Merete et al., 2008; Moorthy et al., 2012; Skarupski et al., 2010; Williams et al., 2005), vitamin B12 (Hintikka et al., 2003; Moorthy et al., 2012), and selenium (Gao et al., 2012; Mokhber et al., 2011; Pasco et al., 2012). However, findings on most of these nutrients require further investigation before definitive conclusions about their relationship with depression can be made.

Diet and its effect on inflammation

There is now strong evidence in human studies that adherence to a Mediterranean diet is associated with reduced inflammatory markers (Camargo et al., 2012; Richard et al., 2012; Urpi-Sarda et al., 2012). In a study on people with metabolic syndrome, five weeks on a Mediterranean diet corresponded with lowered plasma CRP and an arbitrary inflammatory score that included CRP, IL-6, IL-18, and TNF-α. These changes were independent of any weight loss (Richard et al., 2012). Compared to participants placed on a low-fat diet, one year on a Mediterranean diet was associated with lowered plasma concentrations of IL-6, and two TNF receptors (Urpi-Sarda et al., 2012). In contrast, intercellular adhesion molecule-1 and TNF receptor concentrations were increased in people consuming a low-fat diet. In another intervention study, postprandial inflammatory gene expression in mononuclear cells decreased after three weeks on either a Mediterranean diet enriched with olive oil, a diet rich in saturated fatty acids, or a low-fat/high-carbohydrate diet enriched with ω-3 PUFU compared to the other diets (Camargo et al., 2012; Yubero-Serrano et al., 2012)). Luciano and colleagues (2012) also found that CRP levels were lower in an elderly population on a Mediterranean diet compared to a standard 'healthy diet' comprising a high intake of fruits and low consumption of eggs, spirits or liqueurs, and meats such as bacon, pork, lamb, and sausages .

In relation to the anti-inflammatory effect of PUFAs, in a recent review of twenty-six randomised clinical trials, dietary ω-3 EFAs were found to be associated with lower plasma biomarker levels, reflecting lower levels of inflammation and endothelial activation (e.g., IL-6, CRP, TNF- α, sICAM-1 and GM-CSF) in cardiovascular disease and other chronic and acute diseases. Calder (2012) recently concluded that fatty acids were able to partly inhibit a number of aspects of inflammation including leukocyte chemotaxis, adhesion molecule expression and

leukocyte-endothelial adhesive interactions, production of eicosanoids from arachidonic acid, production of inflammatory cytokines, and T cell reactivity.

Diet and its effect on neurotransmitters

Diet quality is important in the production of monoamines such as serotonin and dopamine and can influence receptor sensitivity and neurotransmitter transporters. In animal studies, semi-starvation on a high carbohydrate or protein diet affected serotonin turnover in the brain (Schweiger et al., 1989). In addition, the consumption of sugar as part of a meal (Inam et al., 2006) or eating a high-carbohydrate diet (Buwalda et al., 2001) influenced 5-HT_{1A} receptor sensitivity; and one week on a high fat, low carbohydrate diet decreased serotonin release in the hypothalamus (Banas et al., 2009). In contrast, the acute intake of a carbohydrate-rich food increased brain tryptophan and consequent brain serotonin levels (Fernstrom and Wurtman, 1971). This was likely due to carbohydrates acutely increasing brain tryptophan availability compared to other large neutral amino acids (Wurtman and Wurtman, 1995).

Dopaminergic systems are also influenced by diet as the consumption of combinations of dietary fat and sugar reduced D_2 receptor signalling (Pritchett and Hajnal, 2011), the intake of a high fat diet altered dopamine-related gene expression (Lee et al., 2010; Vucetic et al., 2012), a high-fat diet during early life altered biochemical markers of dopamine signalling in the nucleus accumbens (Teegarden et al., 2009), and the long-term consumption of a low protein-high carbohydrate diet decreased D_2 dopamine receptor density (Hamdi et al., 1992). Striatal dopamine levels were also increased in rats supplemented with strawberry, spinach, or vitamin E (Martin et al., 2000).

Other nutrients which are altered in patients with major depression and that can influence neurotransmitter production include tryptophan (and other large neutral amino acids: valine,

leucine, isoleucine, phenylalanine and tyrosine) (Maes et al., 2011d; Markus, 2008; Toker et al., 2010), folic acid (Miller, 2008; Stahl, 2008), zinc (Cichy et al., 2009; Szewczyk et al., 2011; Szewczyk et al., 2009), vitamin B12 (Bottiglieri, 1996; Deana et al., 1977), vitamin B6 (Calderon-Guzman et al., 2004; Demisch and Kaczmarczyk, 1991; Hartvig et al., 1995) and iron (Baumgartner et al., 2012; Burhans et al., 2005; Coe et al., 2009). Omega-3 EFAs are also able to modify monoaminergic neurotransmission (Chalon, 2006; Su, 2009).

Diet and its effect on oxidative stress

Given the crucial role that diet plays in antioxidant intake, it comes as no surprise that diet quality influences levels of oxidative stress. In animal studies, rats fed a high-sugar/high-fat diet had increased lipid peroxidation in the brain (Ribeiro et al., 2009; Stranahan et al., 2011), elevated plasma malondialdehyde (MDA) concentrations (a marker of lipid peroxidation) (Panchal et al., 2011) and increased mRNA expression levels of genes involved in ROS production in both the liver and adipose tissue (Matsuzawa-Nagata et al., 2008). In obese adults with metabolic syndrome, reducing energy intake by 2000kJ, mainly via carbohydrate restriction, was associated with decreased oxidative stress and increased levels of antioxidant markers, alpha-tocopherol and ceruloplasmin (Skalicky et al., 2009). However, placing adults with metabolic syndrome on a 12-week high-fat diet or low-fat, high complex-carbohydrate diet had no effect on markers of oxidative stress and inflammation (Petersson et al., 2010).

The Mediterranean diet is associated with increased circulating plasma antioxidant levels and decreased oxidative stress (Azzini et al., 2011; Esposito et al., 2011; Yubero-Serrano et al., 2011). The protective properties of this diet may be derived not only from its increased antioxidant concentration but also through its high raw food intake, lower production of cooking-related oxidants and consequent decreased use of nutritional and endogenous antioxidants, and increased fibre intake (Ghiselli et al., 1997). Olive oil, the main source of fat

in the Mediterranean diet, is also effective in lowering lipid peroxidation and oxidative stress (Alarcon de la Lastra et al., 2001; Fito et al., 2007)

Diet and its effect on neuroprogression

Diet quality is important for the brain given its capacity both to enhance neurogenic factors and to influence rates of neurodegeneration. In animal studies, brain levels of BDNF decreased in rats maintained on a high carbohydrate diet (Maioli et al., 2012) and high fat diet (Yamada-Goto et al., 2012). Human trials have also demonstrated a relationship between diet and BDNF. Compared to a low-fat diet, adherence to a Mediterranean diet was associated with an improvement in plasma BDNF concentration in individuals with depression (Sanchez-Villegas et al., 2011). In healthy adults, a high-fat meal decreased plasma BDNF by almost 30% (Karczewska-Kupczewska et al., 2011). The importance of diet on neuroprogression is further confirmed by a study on insulin-resistant, overweight and obese subjects where serum BDNF levels increased after three months on a reduced calorie diet (Araya et al., 2008).

Investigations into the potential effects of ω-3 PUFAs have revealed that they may also play a role in neuroprogression. In animal studies, ω-3 PUFAs supplementation provided protection against reduced plasticity and normalised BDNF after traumatic brain injury (Wu et al., 2004). During pregnancy and lactation, supplementation with ω-3 PUFAs protected levels of BDNF and nerve growth factor (NGF) in female rats when they consumed a micronutrient-imbalanced diet (Sable et al., 2012), while brain levels of BDNF decreased during diets deficient in ω-3 PUFAs (Bhatia et al., 2011; Rao et al., 2007). In an human open-label trial, 3 months of ω-3 PUFAs supplementation increased serum BDNF levels and prevented posttraumatic distress after accidental injury in patients presenting at an intensive care unit (Matsuoka et al., 2011). However, in a randomised, double-blind, placebo-controlled

study of diabetic patients with major depression, 12 weeks of ethyl-EPA supplementation or placebo, in addition to ongoing antidepressant therapy, failed to increase serum BDNF levels (Bot et al., 2011).

Diet and its effect on the HPA axis

Diet composition and timing have a significant influence on acute cortisol secretion due to the primary role of cortisol in gluconeogenesis. However, the long-term effect of diet on HPA activity is not well understood. In a study on women living in a Mediterranean area, a disturbed HPA axis was associated with a higher content of fat and saturated fatty acids in the diet. In contrast, adherence to a dietary pattern closer to the Mediterranean diet was linked with smaller HPA axis disturbances (Garcia-Prieto et al., 2007). Investigations into the effect of ω-3 PUFAs on HPA activity have also provided some evidence of their capacity to lower cortisol activity. For example, Delarue et al. (2003) showed that after 3 weeks on a diet supplemented with ω-3 PUFAs, levels of plasma noradrenaline and cortisol stimulated by mental stress were significantly blunted. In another study on patients with major depression, serum cortisol levels decreased after 8 weeks of treatment with EPA alone or in combination with fluoxetine (Jazayeri et al., 2010). Finally, intravenous lipopolysaccharide-induced adrenocorticotropic hormone (ACTH) and cortisol plasma levels decreased significantly in healthy subjects supplemented with one month of fish oil compared to placebo (Michaeli et al., 2007).

Diet and its effect on mitochondria

Mitochondrial dysfunction is influenced significantly by nutrition (Civitarese et al., 2007; Hepple, 2009; Page et al., 2010; Vitetta and Anton, 2007). Increased fatty acid exposure, resulting from high fat diets or overfeeding, is linked both with decreased mitochondrial number and markers of oxidative phosphorylation. Conversely, caloric restriction can

stimulate mitochondrial biogenesis by elevating the transcriptional processes that regulate mitochondrial mass, improve mitochondrial efficiency, activate ROS scavenging mechanisms, and lower ROS production (Civitarese et al., 2007). Dietary antioxidants or caloric restriction, as well as chemical antioxidants, can lower mitochondrial ROS production (Vitetta and Anton, 2007). Nutrients such as CoQ10, vitamin B2 and l-carnitine also have a significant influence on mitochondrial metabolism (Gardner and Boles, 2011).

The relationship between sleep and depression

In the general population approximately 30% of people report symptoms of insomnia, 10 to 20% describe dissatisfaction with sleep, and approximately 6% have a formal diagnosis of insomnia (Leger et al., 2000; Ohayon, 2002). These rates are significantly increased in major depression, with as high as 90% of patients reporting sleep disturbances (Motivala et al., 2006; Riemann and Voderholzer, 2003). Insomnia is also one of the most common prodromal features of depression with sleep symptoms preceding an episode of depression in 40% of cases. A history of persistent insomnia is also associated with a significantly increased risk of developing a new depressive episode (Taylor et al., 2005). In a recent meta-analysis, compared to people with no sleep difficulties, non-depressed people with insomnia were predicted to have a twofold increased risk of developing depression (Baglioni et al., 2011). Depressed patients suffering from insomnia also have a poorer response to treatment and are at increased risk of relapse (Dombrovski et al., 2008).

Further support for a relationship between sleep and depression is provided by studies documenting improvements in mood and depressive symptoms following insomnia-specific interventions. For example, in a randomised controlled study, Manber and colleagues (2008) found that augmenting antidepressant medication with a symptom-focused cognitive-behavioural therapy for insomnia (CBTI) enhanced treatment outcomes in participants with

co-morbid major depression and insomnia. Compared to participants allocated to control treatment, people receiving CBTI experienced significantly greater remission rates in both depression (61.5% vs 33.3%) and insomnia (50% vs 7.7%). In women with insomnia and breast cancer, CBTI was also more effective in improving sleep, depression and anxiety symptoms than a control condition (Savard et al., 2005). Eight weeks of mindfulness-based cognitive therapy for treating insomnia symptoms also improved sleep, anxiety and depressive symptoms in patients with an anxiety disorder (Yook et al., 2008).

Sleep and its effect on inflammation

Sleep difficulties increase inflammatory mediators; conversely elevated inflammatory molecules heighten the risk of sleep problems. In particular, IL-1, IL-6 and TNF-α may be directly involved in sleep regulation (Santos et al., 2007). Data derived from electrophysiological, biochemical and molecular genetic studies demonstrate that these cytokines are sleep regulatory, as they support the regulation of spontaneous sleep-wake behaviour (Opp, 2005). Other cytokines that may also be involved in the regulation of sleep include IL-2, IL-8, IL-15, IL-18, epidermal growth factor, acidic fibroblast growth factor, colony stimulating factor, and interferons (Krueger, 2008).

In patients with major depression, difficulty initiating sleep correlated with increased pre-sleep levels of IL-6 (Motivala et al., 2005). In a study on 210 healthy young men and women, difficulty falling asleep was related to higher morning levels of CRP and IL-6, but only in women (Suarez, 2008). Sleep disturbances also occur in up to 30% of patients with chronic hepatitis C undergoing IFN-α therapy (Sockalingam et al., 2010), and its administration reduces sleep continuity and depth and induces a sleep pattern consistent with insomnia and hyperarousal (Raison et al., 2010b). Studies on patients diagnosed with primary insomnia offer

additional evidence for the relationship between sleep and inflammation, as circulating levels of IL-6 and TNF are higher than in healthy sleepers (Burgos et al., 2006; Vgontzas et al., 2002).

Sleep restriction studies in animals and humans provide further confirmation for the association between sleep and inflammation. Although the relationship is not necessarily linear, there is evidence that in humans, sleep restriction increases levels of IL-6, TNF-α, CRP and IL-1β (Motivala, 2011; van Leeuwen et al., 2009; Vgontzas et al., 1999; Vgontzas et al., 2004). Five days of sleep deprivation in healthy adults also modified a number of kynurenine pathway metabolites in healthy adults, including 5-hydroxyindoleacetic acid (5-HIAA), xanthurenic acid and anthranilic acid (Kuhn et al., 1968).

Sleep and its effect on neurotransmitters

Surprisingly little research on the influence of sleep on monoamines such as serotonin and dopamine has been conducted, although sleep restriction may disrupt systems associated with monoamine communication. In an animal study, desensitisation in serotonin receptors was detected after eight days of sleep restriction. Despite unlimited recovery sleep, this desensitisation persisted for at least seven days (Roman et al., 2005b), and was independent of adrenal hormones (Roman et al., 2006). In addition, Novati and colleagues (2008) demonstrated that exposure to a schedule of chronic, partial sleep deprivation reduced sensitivity of $5HT_{1A}$ receptors and/or receptors for CRH (Novati et al., 2008).

Sleep and its effect on oxidative stress

It has been proposed that cerebral free radicals accumulate during wakefulness and are removed during sleep (Reimund, 1994). This has been supported by animal studies where sleep loss caused oxidative damage in the brain (Ramanathan et al., 2002; Suer et al., 2011) and increased lipid peroxidation (Thamaraiselvi et al., 2012). However, some animal studies have found that one to two weeks of sleep deprivation had no effect on oxidative stress in any brain

region, including protein oxidation and lipid peroxidation (D'Almeida et al., 1997; Gopalakrishnan et al., 2004). These inconsistent findings are likely a reflection of differing sleep restriction protocols, and different markers of oxidative stress measured across studies.

Most studies on oxidative stress in clinical sleep research have focused on obstructive sleep apnoea syndrome, which is known to increase oxidative stress produced by recurrent episodes of ischemia-reperfusion injury (Kent et al., 2011; McNicholas, 2009). However, several studies have also linked oxidative stress with insomnia. For example, levels of thiobarbituric acid reactive substances were elevated in postmenopausal women with insomnia, although blood concentrations of catalase, superoxide dismutase, and glutathione were found to be normal (Hachul de Campos et al., 2006). In an investigation on participants with primary insomnia, significantly lower GSH-Px (selenium-containing antioxidant enzyme) activity and higher MDA levels were found compared with controls (Gulec et al., 2012). Further evidence of a relationship between sleep and oxidative stress is provided by a study revealing increased levels of myeloperoxidase-modified low-density lipoprotein following five nights of sleep restriction in healthy males (Boudjeltia et al., 2011).

Sleep and its effect on neuroprogression

Sleep problems may also contribute to depressive symptomatology via their effect on brain structure, neurogenesis and, in particular, hippocampal function (Lucassen et al., 2010; Meerlo et al., 2009; Novati et al., 2011). Experimental studies show that prolonged sleep restriction or disruption affects hippocampal integrity (Guzman-Marin et al., 2006; Kopp et al., 2006; McDermott et al., 2003; Roman et al., 2005a). For example, in young male rats, one month of chronic sleep restriction reduced dorsal hippocampal volume by 10% (Novati et al., 2011). Hippocampal cell proliferation was also affected by a single day of sleep deprivation in rats (Roman et al., 2005a). Clinical studies have also reported a reduction in hippocampal volume

in primary insomnia and sleep apnoea (Morrell et al., 2003; Riemann et al., 2007). Insomnia severity in a sample of patients with post-traumatic stress disorder was also associated with decreased volume in the CA3/dentate hippocampal subfield (Neylan et al., 2010).

While sleep restriction itself may not be neurotoxic, it may enhance neuronal sensitivity to subsequent excitotoxic insults. Novati and colleagues (2012) found that after 30 days of sleep restriction in rats, there were no adverse effects on cholinergic cells in the nucleus basalis magnocellularis (NBM). However, an injection of a neurotoxic dose of N-methyl-d-aspartate into the NBM caused an accentuated loss of cholinergic NBM cells and cortical fibres in the sleep-restricted rats compared to controls. Thus, chronic sleep restriction may constitute a mild threat to the brain that does not lead to neurodegeneration by itself but increases vulnerability to subsequent neurotoxic challenges.

Sleep and its effect on the HPA axis

Insomnia appears to be associated with hyperarousal. In a study on patients with chronic insomnia, 24-hour urinary cortisol levels correlated positively with total wake time. Sleep quality also correlated negatively with urinary levels of catecholamine metabolites, thereby suggesting disturbances in both limbs of the stress system (i.e., the HPA axis and the sympathetic system) (Vgontzas et al., 1998). In another study, ACTH and cortisol secretions were significantly higher in insomniacs compared with normal controls, with greatest elevations in the evening and first half of the night. Cortisol levels were also positively correlated with the severity of reported sleep disturbance (Vgontzas et al., 2001). Increased evening and nocturnal plasma cortisol concentrations were also observed in patients with primary insomnia, with a strong positive correlation between evening cortisol secretion and the number of nocturnal awakenings both in insomniac patients and controls (Rodenbeck and Hajak, 2001).

Findings in sleep deprivation and restriction studies are less consistent, with several studies reporting mild elevations of cortisol (Leproult et al., 1997; Spiegel et al., 1999) while others have found no change or even slightly decreased levels (Follenius et al., 1992; Kant et al., 1984). In several animal studies, sleep deprivation led to mild activations of the HPA axis and elevated plasma levels of glucocorticoids (Meerlo et al., 2002; Suchecki et al., 1998), whereas others found little or no effect of acute sleep deprivation on glucocorticoid levels (Rechtschaffen et al., 1983). According to Meerlo et al. (2008) the available data from studies in laboratory animals suggest that sleep restriction may gradually change certain brain and neuroendocrine systems in a manner similar to that seen in stress-related disorders such as depression.

Sleep and its effect on mitochondria

Because of the important role of sleep on oxidative stress, it would seem logical to assume that mitochondria will be adversely affected by sleep deprivation. In support of this, sleep deprivation in mice reduced the activity of the complex I, II and III enzymes of the mitochondrial electron transport chain. Complex II and II-III activity was particularly decreased in the hypothalamus of mice during 24-hour recovery sleep (Andreazza et al., 2010). In a model developed by Andreazza et al. (2010), it was proposed that sleep restriction may lead to mitochondrial dysfunction which, in turn, increases the production of ROS, leading to increased oxidative damage to lipids, protein and DNA.

The relationship between exercise & depression

Depression is commonly associated with low levels of physical activity. While data derived from epidemiological and correlational studies do not necessarily confirm causation, a consistent relationship does exist across a number of populations. In adults, an active lifestyle was associated with reduced depressive symptoms independent of education and physical

health status. This relationship was stronger in women and those aged 40 years and older (Stephens, 1988). In overweight/obese adults, a reduced risk of depression was associated with increasing moderate-to-vigorous-intensity physical activity and decreasing sedentary time (Vallance et al., 2011). Another study on data from over 4,000 men and women aged 20 years or more confirmed that adults with depression spent significantly less time both in light and moderate physical activity than non-depressed adults (Song et al., 2012). In a longitudinal study of over 9,000 people, regular physical activity was associated with a reduced likelihood of depressive symptoms at follow-up (Azevedo Da Silva et al., 2012).

Although not as extensive, investigations into sedentary behaviours have also largely confirmed a positive relationship with depression. In a systematic review of seven observational and four intervention studies on adult populations, Teychenne and colleagues (2010) confirmed that, on balance, sedentary behaviours such as watching television or using the computer were associated with an increased risk of depression. However, evidence was limited by methodological weaknesses in most studies.

The efficacy of exercise as a treatment for depression is summarised in over a dozen recent reviews. In a meta-analysis on supervised and unsupervised physical activity interventions among healthy adults, Conn (2010) concluded that physical activity interventions had a moderate inhibitory effect on depressive symptoms in adults with and without clinical depression (mean effect size of 0.37 for supervised and 0.52 for unsupervised physical activity studies). Carek and colleagues (2011) maintained from a review of the literature that exercise compared favourably to antidepressant medications as a first-line treatment for mild-to-moderate depression and also improved depressive symptoms when used as an adjunct to medications. Similar antidepressant effects were also found in trials comparing exercise with cognitive-behavioural therapy (Rimer et al., 2012). Despite these positive findings there is a

paucity of research demonstrating long-term beneficial effects of exercise in patients with clinical depression (Krogh et al., 2011).

Exercise and its effect on inflammation

Although a single bout of exercise provokes an acute inflammatory response, primarily in IL-6 (release from muscle increases up to 100-fold during contractile exercise), exercise is followed by an increase in anti-inflammatory cytokines (Pedersen and Fischer, 2007) and a decreased production of the pro-inflammatory cytokines TNF-α and IL-1β (Pedersen et al., 2003). Data also suggest that exercise-induced IL-6 inhibits TNF-α production in the presence of low-grade inflammation (Starkie et al., 2003).

Four recent reviews have primarily revealed anti-inflammatory effects from long-term exercise (Beavers et al., 2010; Mathur and Pedersen, 2008; Ploeger et al., 2009; Thomas and Williams, 2008). In a systematic review of 19 studies on the inflammatory effects of acute and chronic exercise in children and adults, Ploeger et al. (2009) concluded that training programs can attenuate chronic inflammation in some patients with chronic inflammatory disease; however, the exercise training-induced response appeared highly dependent on the type of disease, severity of the disease and the frequency, duration and intensity of the exercise intervention.

Lower inflammatory biomarker concentrations, particularly CRP, and to a lesser extent IL-6, are observed across a wide range of individuals performing more frequent and intense physical activity (Plaisance and Grandjean, 2006; Taaffe et al., 2000). This inverse relationship between CRP and physical activity is consistently seen in men, and to a lesser extent in women (Beavers et al., 2010). In adults, investigations using self-reported measures of physical activity have demonstrated that physically-active individuals have CRP concentrations 19–35% lower than less active individuals (Plaisance and Grandjean, 2006). While these

inflammatory markers are attenuated following adjustment for adiposity, a significant relationship between inflammatory biomarkers and physical activity persists (Abramson and Vaccarino, 2002).

In sum, while most studies demonstrate anti-inflammatory effects of exercise in adults and children, the relationship is influenced by a number of factors including the population studied, the type, frequency and duration of exercise, pre-existing medical conditions and initial levels of inflammation. Thus, further studies are required to enable more definitive conclusions, particularly in patients suffering from depression.

Exercise and its effect on neurotransmitters

The antidepressant effects of exercise may be due to its capacity to modify monoamine communication. In animal studies, running increased plasma free tryptophan, brain tryptophan, and levels of the serotonin metabolite, 5-HIAA (Bailey et al., 1993; Chaouloff et al., 1985). Human trials also provide evidence of exercise and its serotonin-enhancing effects. For example, untrained participants randomly assigned to an aerobic exercise group experienced greater changes in serum serotonin levels compared to those in a stretching-control group (Wipfli et al., 2011). Tryptophan availability, the precursor to serotonin, is also increased after acute exercise (Melancon et al., 2012). Three weeks of exercise training also influenced serotonin receptors and serotonin transporters in sedentary males as demonstrated by increased levels of 5-HT transporters (5-HTT) and 5-HT_{2A} receptors on isolated platelet membranes. In contrast, four weeks of excessive training in well-trained athletes did not change 5-HTT, and 5-HT_{2A} receptor density declined. This suggests that the impact of exercise on serotonin neurotransmission may depend on the training state of athletes and extent of exertion (Weicker and Struder, 2001).

Exercise is also able to modify dopamine and noradrenergic transmission as evidenced by increased tyrosine hydroxylase expression (Foley and Fleshner, 2008; Kim et al., 2011), elevated striatal dopamine D_2 receptor expression (Vuckovic et al., 2010) and increased noradrenaline levels (Dishman, 1997) in rats exposed to chronic exercise. However, acute exercise comprising 30 minutes of vigorous exercise in healthy adult volunteers with a history of regular exercise did not change synaptic dopamine concentrations (Wang et al., 2000).

Exercise and its effect on oxidative stress

There is mounting evidence to suggest that exercise is accompanied by an increased generation of free radicals, resulting in measurable elevations in oxidative stress biomarkers after both acute aerobic (Benitez-Sillero et al., 2011; Bloomer, 2008; Fogarty et al., 2011) and anaerobic exercise (Bloomer and Goldfarb, 2004; Pittaluga et al., 2006; Vollaard et al., 2005). Given the substantial evidence for the protective effects of exercise on oxidative stress-associated diseases, this seems paradoxical. However, it is argued that chronic exercise leads to exercise-induced adaptation and resistance (Cooper et al., 2002; Radak et al., 2008). The exercise-induced ROS formation evokes specific adaptation, comprising up-regulation in endogenous antioxidant defences, increased antioxidant/oxidative damage-repairing enzyme activity, increased resistance to oxidative stress, and lowered levels of oxidative damage. This adaptive response seems to be systemic, affecting skeletal muscle, liver, and the brain (Radak et al., 2008). Gomez-Cabrera et al (2008) argue that because exercise results in an up-regulation of powerful antioxidant enzymes, exercise itself can be considered an antioxidant despite generating free radicals.

Exercise and its effect on the HPA axis

The relationship between exercise and HPA activity is complex as it is influenced by duration, type, intensity and chronicity of exercise; characteristics of the stressor used; and

characteristics of the population studied (Campeau et al., 2010; Leal-Cerro et al., 2003; Mastorakos et al., 2005; Stranahan et al., 2008). In an animal study, four weeks of swimming exercise was associated with reduced levels of serum corticosterone and depressive behaviours in rats exposed to high levels of glucocorticoids prenatally (Liu et al., 2012a). In another study, the HPA axis response to lower-intensity stressors decreased in rats exposed to 6 weeks (but not 1 or 3 weeks) of intermittent, voluntary wheel running, although no change occurred following exposure to more intense stressors (Campeau et al., 2010). The complexity of the relationship between exercise and HPA responsivity was further demonstrated by Droste et al. (2003) who reported that HPA responses in exercising mice were differently influenced by the stressor used and the novelty of the environment.

Investigations into the relationship between exercise and HPA activity in human populations have primarily examined the effect of acute activity on measures such as cortisol and ACTH. Studies on the influence of chronic exercise on HPA activity, and in particular on the HPA response to stressors, are sparse. In general, acute exercise elevates cortisol levels, although this most consistently occurs following moderate-to-severe intensity activity (Hill et al., 2008). In a study on women of varying age and fitness, ACTH levels recovered slowly in older women, particularly those with low fitness levels (Traustadottir et al., 2004). In a study on female adolescents with mild-to-moderate depression, 8 weeks of an exercise regimen improved depressive symptoms and was associated with reductions in 24 hour urinary cortisol levels (Nabkasorn et al., 2006). In another study on patients with chronic low back pain, twelve weeks of high-intensity aerobic exercise was associated with reductions in pain, enhanced mood and improvements in HPA responsiveness to the dexamethasone suppression test (Chatzitheodorou et al., 2008).

Exercise and its effect on neuroprogression

Evidence of the beneficial effects of exercise on brain function is summarised in three recent reviews (Cotman et al., 2007; Dishman et al., 2006; Vivar et al., 2012). Exercise is associated with enhanced adult hippocampal neurogenesis and increased activity-dependent synaptic plasticity. According to Cotman et al. (2007), enhanced hippocampal neurogenesis and increased synaptic plasticity are the most reproducible effects of exercise in the rodent brain. In both young and old animals, exercise stimulated neural progenitor populations, increased the number of new neurons, and promoted survival of these new cells (Brandt et al., 2010; Olson et al., 2006; Wu et al., 2008). In animal studies, exercise also increased BDNF in several brain regions, and there was increased insulin-like growth factor-1 (IGF-1) gene expression and peripheral circulating levels of IGF-1 (Ding et al., 2006; Schwarz et al., 1996). In a review on the effects of exercise on peripheral BDNF in human subjects, it was concluded that exercise temporarily elevated basal BDNF and possibly up-regulated BDNF cellular processing (i.e. synthesis, release, absorption and degradation) (Knaepen et al., 2010). However, there have been no reported findings of long-lasting BDNF responses to acute exercise or training.

Human studies on the effects of exercise-induced BDNF changes in depressed populations are still preliminary, although BDNF levels were transiently increased in elderly women with remitted major depression (Laske et al., 2010) and in unmedicated patients suffering from major depressive disorder (Gustafsson et al., 2009).

Exercise and its effect on mitochondria

An accumulating body of literature has demonstrated that endurance exercise effectively stimulates mitochondrial biogenesis in a wide range of tissues including skeletal muscle, adipose tissue, liver, brain, and kidney (Little et al., 2011). Vina et al. (2009) concluded that exercise, and particularly aerobic exercise, activated mitochondriogenesis in young animals,

although its influence on older animals required further investigation. Eight weeks of treadmill training in a murine model augmented mitochondrial function, as reflected by increased mitochondrial enzyme activities, maximal rate of ATP synthesis in isolated mitochondria, and whole-body maximal O_2 uptake (Chow et al., 2007). Lanza et al. (2009) reviewed a number of studies which demonstrated that older adults enrolled in exercise training programs respond with increased VO_2 peak, mitochondrial content, oxidative enzyme activities, muscle protein synthesis rates, mitochondrial protein gene transcripts, and mitochondrial DNA copy number.

Conclusion and directions for future research

While the importance of lifestyle factors such as diet, exercise and sleep are generally acknowledged in the research literature on major depression, the mechanisms of their potential influence are often not fully appreciated. As illustrated in figure 3, diet, exercise and sleep can influence several physiological pathways associated with depression. A bi-directional relationship likely exists between depression and these lifestyle factors, thereby creating a potentially increasing cycle of influence. Key symptoms of major depression include changes in appetite, sleep, energy and general motivation levels; all likely to have significant effects on diet, exercise and obviously sleep patterns. The importance of these lifestyle factors was highlighted in a recent paper by Jacka et al (2012) who argued that depression should be included under the umbrella of non-communicable diseases influenced by lifestyle factors, with increasing efforts directed toward prevention through the promotion of lifestyle changes.

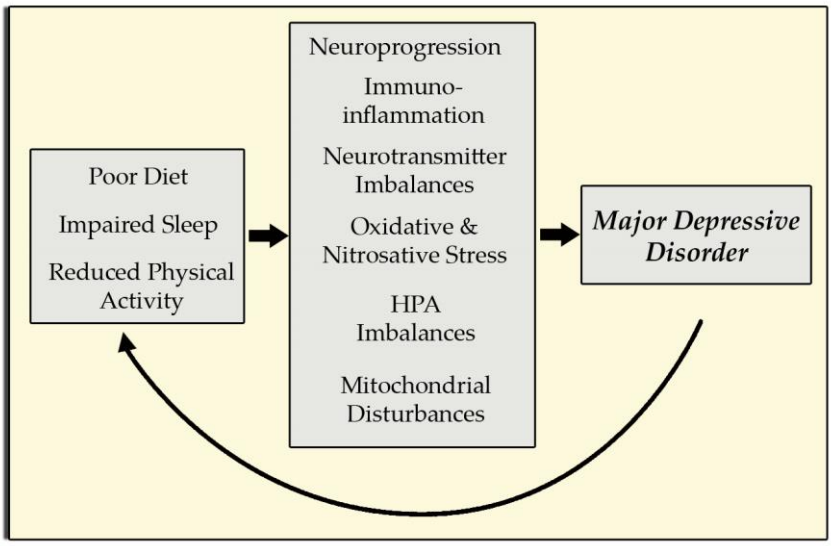

Figure 3. *Potential mechanisms of diet, sleep and exercise on major depression.* Diet, sleep and exercise are associated with depression. These lifestyle factors influence a number of biological processes associated with major depression including neurotransmitter transmission, immuno-inflammation, oxidative and nitrosative stress, HPA balance, neuroprogression and mitochondrial health. Suffering from depression is also likely to lead to changes in diet, sleep and exercise, creating a vicious cycle of change.

While these lifestyle factors are significant in the etiology and maintenance of depression, a multitude of other lifestyle influences may also be important. These include chronic stress, social influences, mental and physical effects associated with medical diseases, alcohol and other drug use, chronic pain and even exposure to sunlight/vitamin D. It is these influences, plus a large array of psychological, genetic and biological factors that often make the treatment of depression difficult. Basic interventions comprising attention towards one cause and/or one biochemical mechanism (e.g., targeting a single neurotransmitter disturbance) makes the goal of remission or recovery less likely. This was highlighted in a recent study where giving simple written recommendations about lifestyle changes for sleep hygiene, physical activity, diet, and sunlight exposure enhanced outcomes to standard antidepressant treatment (Garcia-Toro et al., 2012). Remission/response rates reached 60% in the combined treatment group compared with only 10% in the anti-depressant only group.

Future research needs to be directed toward better understanding the role that diet, exercise, sleep and other lifestyle factors play in depression and other mental health conditions. While this review provides a comprehensive coverage of the research literature, with a specific emphasis on the biological effects of these lifestyle factors on depression, a future more systematic review with well-defined search strategies and inclusion criteria would be beneficial to further elucidate the role these lifestyle factors play in depression, particularly those addressing diet.

A limitation associated with many of the studies reviewed is that significant portions were correlational and/or epidemiological, thereby limiting conclusions about causation. Other influences such as general healthy lifestyle behaviours, socioeconomic status and medical illnesses are examples of confounding factors that may have influenced findings in some studies. Given these and other confounding influences, a significant barrier associated with studies on dietary intervention is being able to accurately provide direct evidence that dietary change causes improvements in mental health. Increasing attention toward randomised, placebo-controlled treatment studies may help to elucidate the mediating roles that these lifestyle factors play in major depression. A paucity of treatment studies has investigated dietary interventions in depressed populations; however, an inherent problem relates to identifying methods to blind such interventions for participants and investigators. While this may be possible with single nutrients or foods, it is likely that the benefits of diet are derived from consuming a range of complementary foods, particularly those characteristic of Mediterranean diets (Ghiselli et al., 1997{Milaneschi, 2011 #1450; Milaneschi et al., 2011). It is also important that increasing attention be given to measuring changes in important biomarkers associated with inflammation, oxidative stress, HPA regulation, neuroprogression, monoamine and mitochondrial function. Measuring changes in biomarkers and assessing their

relationship with affective and behavioural changes should provide a greater understanding of mechanisms of action associated with depression.

Contributors:

Adrian Lopresti conducted a literature search and wrote the first draft of this manuscript. Peter Drummond and Sean Hood reviewed the manuscript and provided feedback, corrections and recommendations on further drafts of this manuscript. All authors contributed to and have approved the final manuscript.

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Obesity and psychiatric disorders: commonalities in dysregulated biological pathways and their implications for treatment

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Abstract

Rates of obesity are higher than normal across a range of psychiatric disorders, including major depressive disorder, bipolar disorder, schizophrenia and anxiety disorders. While the problem of obesity is generally acknowledged in mental health research and treatment, an understanding of their bi-directional relationship is still developing. In this review the association between obesity and psychiatric disorders is summarised, with a specific emphasis on similarities in their disturbed biological pathways; namely neurotransmitter imbalances, hypothalamus–pituitary–adrenal axis disturbances, dysregulated inflammatory pathways, increased oxidative and nitrosative stress, mitochondrial disturbances, and neuroprogression. The applicability and effectiveness of weight-loss interventions in psychiatric populations is reviewed along with their potential efficacy in ameliorating disturbed biological pathways, particularly those mediating inflammation and oxidative stress. It is proposed that weight loss may not only be an effective intervention to enhance physical health but may also improve mental health outcomes and slow the rate of neuroprogressive disturbances in psychiatric disorders. Areas of future research to help expand our understanding of the relationship between obesity and psychiatric disorders are also outlined.

List of Abbreviations: BMI, body mass index; BDNF, brain-derived neurotrophic factor; CBT, cognitive behaviour therapy; COX, cyclooxygenase; CNS, central nervous system; CRP, C-reactive protein; HPA, hypothalamus-pituitary-adrenal; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; PTSD, post-traumatic stress disorder; TNF, tumour necrosis factor.

Investigations into the biological mechanisms associated with psychiatric disorders such as major depressive disorder, bipolar disorder, schizophrenia and anxiety disorders have identified several mechanisms specific to each disorder. For example, dysregulation of the neurotransmitter serotonin is associated with major depressive disorder and, to a lesser extent, with several anxiety disorders (Cowen, 2008; Dantzer et al., 2011). Recently, increased attention into the kynurenine pathway has revealed that it is upregulated in major depressive disorder, and interest in its role in other psychiatric disorders such as schizophrenia is underway (Maes et al., 2011d; Myint, 2012; Myint et al., 2012). Other neurotransmitters such as glutamate are linked primarily with schizophrenia, and dopamine with bipolar and psychotic disorders (Abi-Dargham, 2004; Cousins et al., 2009; Seeman, 2009; Steele et al., 2012). Several genetic polymorphisms are also uniquely associated with different psychiatric disorders, such as polymorphisms in the serotonin transporter gene with depression (Kuzelova et al., 2010), and catechol-O-methyl transferase gene polymorphisms with schizophrenia and bipolar disorder (Sagud et al., 2010).

Despite the unique characteristics of each disorder, they share several common dysregulated biological pathways. As illustrated in Figure 1, these include neurotransmitter imbalances; hypothalamus–pituitary–adrenal (HPA) axis disturbances; dysregulated inflammatory pathways; increased oxidative and nitrosative stress and reduced antioxidant defences; neuroprogression resulting in neurodegeneration, apoptosis, reduced neurogenesis and neuronal plasticity; and mitochondrial disturbances (Altamura et al., 2013; Anderson et al., 2013a; Anderson et al., 2013b; Berk et al., 2011; Moylan et al., 2013a; Moylan et al., 2012; Salim et al., 2012; Vieta et al., 2013). These dysregulated pathways interact significantly with each other, and their translation into specific psychiatric disorders is influenced by other biological mechanisms, environmental factors and genetic polymorphisms.

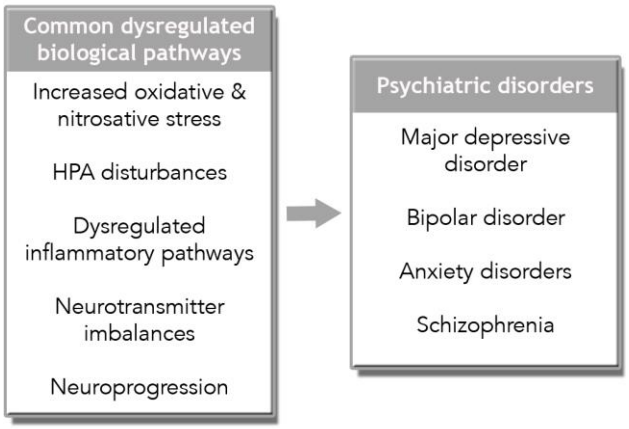

Figure 1. *Common dysregulated biological pathways associated with psychiatric disorders*

While it is acknowledged that these disturbances are influenced by genetic and environmental factors, psychological, lifestyle and social influences are also important (Anderson and Maes, 2013; Leonard and Maes, 2012; Lopresti et al., 2013; Maes et al., 2011c). One often overlooked influence concerns obesity. This review provides an overview of the relationship between obesity and psychiatric disorders, similarities in their disturbed biological pathways, and the potential of weight loss interventions not only to improve general health but also to enhance mental health outcomes in psychiatric patients.

Is there an association between obesity and psychiatry disorders?

Rates of obesity are greater than normal in psychiatric populations, particularly in women (Allison et al., 2009; McElroy, 2009). For example, Daumit et al. (2003) reported that 29% of men and 60% of women with severe and persistent mental illness were obese, compared to 17.7% of men and 28.5% of women in the general population. Dickerson et al. (2006) found that 50% of a female, and 41% of a male psychiatric sample were obese, compared to 27% of women and 20% of men in a non-psychiatric matched comparison group. In a meta-analysis of 15 longitudinal studies, Luppino et al. (2010) concluded that depression was associated with increased rates of obesity. More specifically, a bidirectional association was found between

depression and obesity with obesity increasing the risk of depression and prior depression increasing the likelihood of obesity. Several studies have found that abdominal obesity in particular may be characteristic of depression (Carpiniello et al., 2012; Rivenes et al., 2009; van Reedt Dortland et al., 2013).

After controlling for several demographic influences, Petry et al. (2008) concluded that obesity increased the odds of any mood, anxiety, and alcohol use disorder significantly, as well as any personality disorder, with odds ratios ranging from 1.21 to 2.08. In a large, nationally representative sample, Goldstein et al. (2011) found a nearly two-fold age-, race-, and sex-adjusted increased risk of obesity among adults with bipolar disorder versus controls. Obese participants with bipolar disorder also had greater comorbidity with anxiety disorders, longer depressive episodes, and significantly poorer physical and mental health functioning compared to non-obese people with bipolar disorder.

Possible mediators of the relationship between obesity and psychiatric disorders

Current and past unhealthy dietary patterns are associated both with obesity (Hsiao et al., 2011; Rosenheck, 2008; Schroder et al., 2007) and psychiatric disorders (Jeffery et al., 2009; Sanchez-Villegas et al., 2009; Sanchez-Villegas et al., 2012) . Lower rates of physical activity and increased sedentary behaviours are also commonly observed in currently obese (Bailey et al., 2007; Tucker and Tucker, 2011) and psychiatric patients (Azevedo Da Silva et al., 2012; Song et al., 2012) and are also risk factors for the future development of both these conditions. Rates of sleep disorders such as insomnia and sleep apnoea are also increased in obesity and psychiatric disorders (Costa e Silva, 2006; Kalucy et al., 2013; Krystal et al., 2008; Leger et al., 2000), and both obesity and psychiatric disorders are associated with a greater prevalence of cardiovascular diseases (Stanley and Laugharne, 2012), metabolic disorders (Leonard et al.,

2012; Rotella and Mannucci, 2013; Yau et al., 2012) and autoimmune conditions (Aballay et al., 2013). Early life trauma, including sexual and physical abuse, has also been identified as a risk factor for the development of obesity (Boynton-Jarrett et al., 2012; D'Argenio et al., 2009; Gunstad et al., 2006) and psychiatric disorders (Breslau, 2002; Chou, 2012).

Can psychiatric medications account for the increased rates of obesity in psychiatric populations?

Weight gain is a commonly reported side effect of many psychiatric medications. In a recent meta-analysis, the antidepressants amitriptyline, mirtazapine, and paroxetine were associated with the greatest risk of weight gain, with other investigated antidepressants having only transient or negligible effects on body weight in the short term (Serretti and Mandelli, 2010). However, the effect of each antidepressant may be influenced by several individual characteristics (e.g., sex, BMI, previous medication history, genetic polymorphisms) and generally becomes more evident over the long term (Dent et al., 2012). Weight gain is also a common problem associated with many atypical antipsychotics such as clozapine and olanzapine, and also increases the risk of metabolic disorders such as diabetes mellitus and dyslipidaemia (Dent et al., 2012; Gautam and Meena, 2011; Newcomer, 2005; Rummel-Kluge et al., 2010).

Increasing evidence suggests that genetic factors may be particularly important in medication-induced weight gain. This is supported by monozygotic twin and sibling studies (Wehmeier et al., 2005), and several genetic polymorphisms have also been identified as risk factors for weight gain (Muller et al., 2013). Serotonin and histamine receptors have received most attention as they seem to play important roles in eating behaviour and may contribute to weight gain via their influence on lipolytic activity (Deng et al., 2010). For example, at least 17 studies have reported an association between the 759 T/C SNP in the 5HT2C gene and

antipsychotic medication-induced weight gain. This effect was particularly strong in patients treated with clozapine and olanzapine, both of which have high affinity to 5HT2C receptor (De Luca et al., 2007). The 2548 A/G variant of the leptin gene has also been associated with long-term (but not short term) weight gain (Ellingrod et al., 2007; Templeman et al., 2005).

Although medication-induced weight gain may partly account for the increased prevalence of obesity in psychiatric populations, it seems unlikely to totally explain this relationship. For example, in a systematic review and meta-analysis, Luppino et al. (2010) confirmed that obesity at baseline increased the risk of onset of depression at follow-up. This finding was also supported in a review by Berkowtiz and Fabricatore (2011). Childhood overweight and obesity is associated with an increased risk of mood disorder in adulthood (Sanderson et al., 2011), and higher rates of overweight and obesity have been observed in medication-naïve patients with bipolar disorder (Maina et al., 2008).

Thus, the increased risk of psychiatric disorder in obese individuals is likely caused by a combination of psychological, social, lifestyle, genetic and biological factors, with the latter cause being the primarily focus of this review.

What effect does obesity have on treatment outcomes?

Surprisingly little research has investigated the effects of obesity on treatment resistance in psychiatric disorders; however, studies conducted to date have shown that obesity is associated with an increased likelihood of treatment failure. Studies on antidepressant therapies have found that higher body weight, but not obesity, was associated with a poorer response to fluoxetine (Papakostas et al., 2005), a higher body mass index (BMI) and obesity predicted poorer response to nortripitlyine but had no influence on the response to escitalopram (Uher et al., 2009), and individuals with higher BMI experienced a slower clinical response to general antidepressant treatment (Kloiber et al., 2007). Khan et al. (2007) also

found that depressed, obese men experienced little or no therapeutic benefit from antidepressant treatment. An investigation on patients with rapid-cycling bipolar disorder also showed that obesity was associated with a poorer treatment response to lithium and valproate (Kemp et al., 2010). Inflammation and increased pro-inflammatory cytokine production, commonly observed in obesity, are also associated with a poor antidepressant treatment response (Eller et al., 2008; O'Brien et al., 2007; Yoshimura et al., 2009). No studies have been identified investigating the effect of obesity on psychological and other non-drug treatments for psychiatric disorders.

How obesity influences biological pathways associated with psychiatric disorders

As summarised in Figure 2, studies over the past two decades have confirmed that obesity is associated with increased inflammation, oxidative stress, HPA disturbances, neurotransmitter imbalances, mitochondrial disturbances and neuroprogression.

White adipose tissue, the main site for long-term fat storage in the body, contains adipocytes that secrete a variety of hormones and inflammatory cytokines (referred to as adipocytokines or adipokines). These include leptin, resistin, vistfatin, interleukin-6 (IL-6), tumour necrosis factor- α (TNF-α) and chemokines (Shelton and Miller, 2010). These are all consistently elevated in obesity, as are acute phase proteins such as c-reactive protein (CRP) (Das, 2001; Gregor and Hotamisligil, 2011; Shelton and Miller, 2010). Obesity is also associated with upregulation of the kynurenine pathway, evidenced by reduced concentrations of plasma tryptophan (Breum et al., 2003) and an increased kynurenine/tryptophan ratio (Brandacher et al., 2007). Upregulation in the kynurenine pathway influences neurotransmitter production (particularly serotonin) and is associated with increased

oxidative stress and neurodegeneration. This pathway is dysregulated in major depressive disorder, and may also be important in schizophrenia and bipolar disorder (Myint, 2012).

Fat accumulation is also associated with systemic oxidative stress, demonstrated by elevations in lipid and protein peroxidation (Furukawa et al., 2004; Vincent et al., 2007). An altered mitochondrial energy production, particularly in skeletal muscles (Rogge, 2009), and dysregulation in the HPA axis are also observed in obese people (Duclos et al., 2001; Salehi et al., 2005). Support for neurotransmitter disturbances in obesity is obtained by findings of decreased availability of dopamine D2 receptors in the CNS of obese individuals (Wang et al., 2001; Wang et al., 2009). Animal studies have shown that serotonin transporter mRNA levels are significantly down-regulated in neurons in the dorsal raphe nucleus of obese mice (Collin et al., 2000), while overeating has been associated with decreased release of serotonin in the hypothalamus (Svec et al., 2002). Obesity is also associated with unhealthy diets, excess calorie intake and inactivity, which can influence pathways associated with depression and other psychiatric disorders (Lopresti et al., 2013).

Investigations into structural brain changes has largely confirmed that obese and overweight individuals have a smaller hippocampal size compared to healthy individuals (Fotuhi et al., 2012; Mueller et al., 2012; Raji et al., 2010; Taki et al., 2008). A higher mid-life BMI also increases the rate of hippocampal atrophy in late life (Jagust et al., 2005; Taki et al., 2008). Low total brain volumes are also observed in overweight individuals and in those who have a normal BMI but a large abdominal diameter (Kurth et al., 2012). Brain derived neurotrophic factor (BDNF), which has a key role in regulating neuronal development and synaptic function, also plays a part in the control of energy balance by the central nervous system. BDNF deficiency is associated with increased weight in mice and humans (Noble et al., 2011; Schwartz and Mobbs, 2012).

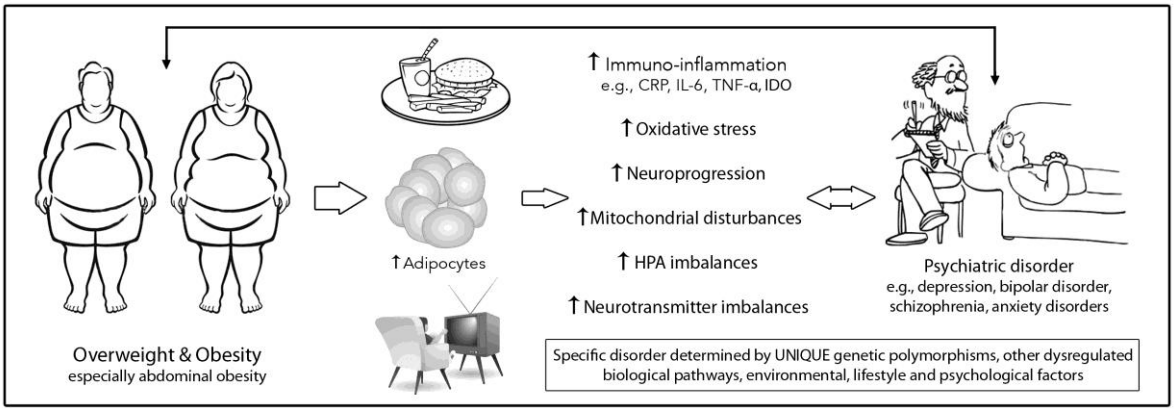

Figure 2. *Obesity and its influence on pathways associated with psychiatric disorders.* Obesity influences several biological pathways associated with psychiatric disorders including immuno-inflammatory processes, oxidative stress, neuroprogression, mitochondrial disturbances, HPA axis imbalances and neurotransmitter imbalances. A bi-directional relationship likely exists (represented by the bidirectional arrow) between obesity and psychiatric disorders, as obesity increases the risk of psychiatric disorders, and suffering from a psychiatric disorder increases the likelihood of obesity. Suffering from both these conditions is likely to have an additive influence on these pathways. While psychiatric disorders share many commonalities in dysregulated pathways, genetic, environmental, lifestyle and psychological factors will determine the specific disorder(s) suffered [c-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), indoleamine 2,3 dioxygenase (IDO)]

Does weight loss improve dysregulated pathways associated with psychiatric disorders?

Weight loss interventions are regularly associated with lower markers of inflammation such as CRP, IL-6 and TNF-α (Bougoulia et al., 2006; Illan-Gomez et al., 2012; Nicklas et al., 2004; Pakiz et al., 2011). These effects are often enhanced when interventions include an exercise component (Pakiz et al., 2011), although this is not always found (Church et al., 2010). Many studies have demonstrated that anti-inflammatory effects of weight loss may not be observed for up to 6 months (Snel et al., 2011), but then continue despite participants gaining weight and returning to baseline weight levels (Olszanecka-Glinianowicz et al., 2012; Snel et al., 2011). After a 5 year follow-up, significant decreases in TNF-α and IL-6 obtained after initial weight loss treatment were maintained. This even occurred in women who regained all their weight (Olszanecka-Glinianowicz et al., 2012). Reductions in inflammatory markers such as CRP and IL-6 have even been observed after weight loss as little as 5% (Imayama et al., 2012), although Madsen et al. (2008) found that over a 3-year period weight loss needed to

exceed 10% to induce a significant improvement in inflammatory markers. Weight loss is also associated with reduced markers of oxidative stress such isoprostane, thiobarbituric acid reactive substances and malondialdehyde (Boesing et al., 2010; Bougoulia et al., 2006; Ozcelik et al., 2005; Wycherley et al., 2008), and increased antioxidant enzymes such as glutathione peroxidase and catalase (Boesing et al., 2010; Bougoulia et al., 2006).

Is weight loss possible in psychiatric patients?

Investigations into weight loss programs on psychiatric populations have confirmed that weight loss is an achievable goal. In a study by Faulconbridge et al. (2012), overweight patients suffering from depression and type 2 diabetes lost 8.6% of their initial weight after a one year intensive lifestyle intervention. Severity of depressive symptoms at baseline did not influence the magnitude of weight lost (Faulconbridge et al., 2012). Obese females diagnosed with major depressive disorder receiving weekly group behavioural weight management for 16 weeks, combined with cognitive behaviour therapy (CBT) for depression, lost 11.4% of their initial weight (Faulconbridge et al., 2011) and, compared to a non-depressed sample, depressed, obese individuals achieved similar weight loss following participation in a behavioural weight loss treatment (Linde et al., 2011). Significant weight loss can also be achieved in depressed and bipolar patients following gastric bypass surgery (Deliopoulou et al., 2013; Malone et al., 2011; Steinmann et al., 2011). Furthermore, taking antidepressant medication prior to surgery did not affect weight loss outcomes at 12 months (Malone et al., 2011).

In patients with schizophrenia and psychotic disorders, weight loss and weight maintenance is also an achievable goal (Daumit et al., 2011; Pendlebury et al., 2007). In a meta-analysis on randomised, controlled, cognitive-behavioural weight loss trials, Bonfioli et al (2012) concluded that in patients with psychosis, a weight loss of 0.98 points in BMI

(corresponding to a loss of 3.12% of initial weight) was demonstrated from pooled data. Weight loss programs can also prevent weight gain associated with antipsychotic use and even promote weight loss (Chen et al., 2009; Gabriele et al., 2009; Menza et al., 2004; Vreeland et al., 2003). In a study by Zhang et al. (2012), patients with psychotic spectrum disorders experienced a greater percent baseline weight loss at 12 months, and greater percent BMI loss at 9 and 12 months than people suffering from other psychiatric disorders and no psychiatric disorder. Furthermore, weight loss of 5% or more occurred in 42.6% of patients with psychotic spectrum disorders compared to 18.4% and 23.0% in patients suffering from other psychiatric disorders and no psychiatric disorders, respectively.

Does weight loss improve mental health?

Investigations into the effect of weight loss on mental health outcomes have primarily investigated its effect on depressive symptoms. In a meta-analysis of 31 studies, Fabricatore et al. (2011) concluded that lifestyle modification was superior to control and non-dieting interventions in reducing symptoms of depression, and was marginally better than dietary counselling and exercise-alone programs. Bariatric surgery in obese individuals also improved symptoms of depression and lowered rates of antidepressant use, but had no effect on anxiolytic use (Rutledge et al., 2012). Intragastric balloon insertion was also effective in lowering depressive symptoms in a subsample of depressed adults (Deliopoulou et al., 2013). Using a depressed population of obese women, participation in a behavioural weight loss program or a combined weight loss and depression program led to a reduction in depressive symptoms and modest weight loss in both groups. Interestingly, there were no differences in outcomes between the two treatment groups (Linde et al., 2011). Little is known about the effect of weight loss programs on mental health outcomes in other psychiatric disorders such as schizophrenia, bipolar and anxiety disorders. However, in a study by Chen et al. (2009) on

patients with schizophrenia and antipsychotic-related obesity, participation in a 10-week multimodal weight control program led to weight loss that was mostly maintained at 12-months follow up. Completers also reported significant improvements in measures of quality of life, general health, bodily pain, depression and other emotional subscales. Significant improvements were also reported in positive and negative symptoms as measured by the positive and negative symptom scale. In a study on obese participants suffering from post-traumatic stress disorder (PTSD), weight loss after a 16-week weight loss intervention was associated with a significant decline in PTSD and depressive symptoms (Deliopoulou et al., 2013).

Conclusion and directions for future research

Psychiatric disorders are common in obese and overweight people, with both disorders sharing several common dysregulated physiological pathways. These include heightened inflammation and oxidative stress, HPA imbalances, mitochondrial disturbances and neurotransmitter imbalances. Both disorders are also associated with neuroprogression as evidenced by decreased neurogenesis and changes in brain structure, particularly in the hypothalamus. Several studies have also confirmed that obesity is associated with increased treatment resistance, although weight loss is achievable in psychiatric patients and is often associated with improvements in mental health symptoms. Weight loss also leads to improvements in a number of physiological pathways that are disturbed in mental health disorders.

It is generally accepted that obesity is caused by an array of genetic, biological, environmental and psychological factors that influence each other. While this review has been limited to the discussion of a few key biological pathways, it is acknowledged that a range of other factors are important in the development and maintenance of the obesity-psychiatric

disorder relationship (Grimm and Steinle, 2011; Karasu, 2012; Power et al., 2007; Soczynska et al., 2011). This genetic-biological-environmental-psychological interaction will significantly influence food choices, activity patterns, hunger and satiety cues, self-regulation around food and exercise, lifestyle habits, belief systems, and numerous physiological processes associated with both obesity and psychiatric disorders. Other hormones which are important but have not been the focus of this review includes leptin, insulin, adiponectin, ghrelin, cholecystokinin, and neuropeptide Y (Grimm and Steinle, 2011; Soczynska et al., 2011).

While our understanding of the relationship and psychiatric disorders is increasing, there remain an array of unanswered questions that require further investigation. These include the following:

1. *Is there a bi-directional relationship between obesity and psychiatric disorders?*

   Research to date, particularly in the area of depression, suggests a bi-directional relationship between obesity and psychiatric disorders (Luppino et al., 2010). Longitudinal studies will help further elucidate this relationship. Does suffering from obesity increase the likelihood of suffering from a psychiatric disorder and, if so, what are the important mechanisms that underlie this? Alternatively, does suffering from a psychiatric disorder increase the likelihood of experiencing future obesity and is this due to medication use or are other biological and lifestyle factors involved? Understanding other mediators involved in the relationship between obesity and psychiatric disorders such as dietary and lifestyle factors will also be important areas of investigation.

2. *If weight loss is an important treatment goal in psychiatric populations, what is the most appropriate form of intervention?*

   Sustained weight loss remains an elusive goal for the general population; however, studies do show positive health benefits associated with modest weight losses of 5 to 10 percent (Imayama et al., 2012; Madsen et al., 2008). What is most promising is that many markers of

inflammation and oxidative stress remain low even after all weight lost has been regained (Olszanecka-Glinianowicz et al., 2012; Snel et al., 2011). However, the question remains as to the most appropriate weight loss intervention for psychiatric populations. A range of options are available including behavioural weight loss programs (with or without an exercise component), individual and/or group formats, inpatient or outpatient programs, weight loss medications, and bariatric surgeries. The length and intensity of treatment to achieve optimal results in psychiatric populations also requires investigation.

3. *Does weight loss have positive effects for all psychiatric disorders and symptoms?*

   Investigations into the mental health benefits of weight loss have primarily investigated its effect on depressive symptoms. Given the positive influence of weight loss on a number of physiological pathways found to be disturbed in a range of psychiatric disorders, weight loss may also have positive benefits on manic, psychotic, anxiety and other affective and behavioural symptoms. However, this is an area that has received very little attention.

4. *Are mental health benefits from weight loss short-lived or long standing?*

   The durability of positive changes in psychiatric symptoms following weight loss requires investigation. Most studies have assessed changes immediately following a weight loss intervention. However, long-term follow-up studies are required to determine whether these changes persist.

5. *Are improvements in psychiatric symptoms the result of changes in physiological, psychological, or environmental processes, or a combination?*

   If mental health improvements occur following weight loss treatments, an understanding into the specific mechanisms that underlie change would be useful. Are positive changes the result of changes in inflammatory, neurogenic and oxidative stress pathways or are they mediated by changes in diet, physical activity, belief systems, social acceptance, or

other lifestyle factors? For example, exercise is an effective treatment for moderate depression and anxiety, and healthier diets, particularly adherence to a mediterranean diet, is associated with improvements in mental health (Lopresti et al., 2013; Moylan et al., 2013a). Changes in these areas are major components of weight- loss programs. To answer this question, ongoing measurement of psychological, social, lifestyle, and behavioural changes, and measurement of relevant biomarkers over time will be required.

6. *How much weight loss is required for mental health benefits to be achieved?*

   This will assist practitioners to develop appropriate treatment goals with patients. Given the increasing awareness of lifestyle factors such as diet, exercise and sleep in mental health problems (Jacka et al., 2012; Lopresti et al., 2013), it may be that weight loss is not an essential outcome for mental health benefits, but rather the crucial component is lifestyle changes.

7. *Are there dangers associated with weight loss interventions undertaken in psychiatric populations?*

   Developing appropriate guidelines for inclusion in weight loss programs will be important. Are there particular psychiatric disorders where weight loss interventions are not appropriate? Are there specific characteristics that would increase the likelihood of harm associated with participation in a weight loss program, or should participation be open to anyone who is motivated to attend?

8. *What inflammatory and oxidative stress changes occur in psychiatric populations after weight loss?*

   Most research into the effects of weight loss on inflammatory and oxidative stress biomarkers has been undertaken in non-psychiatric populations. Resolving this is important as there is substantial evidence of increased inflammation and oxidative stress in psychiatric disorders. The relationship between changes in these biomarkers and

mental health symptoms will also provide valuable information for researchers and clinicians.

9. *Do obese and overweight psychiatric populations require specialised or additional interventions to enhance treatment gains?*

   This issue is particularly pertinent given the increasing awareness of neuroprogression in both psychiatric disorders and obesity. Potentially, suffering from both conditions may increase neuroprogressive pathways and lead to worsening treatment outcomes, relapse or treatment resistance. Adjunct interventions that may be considered include the addition of anti-inflammatory drugs such as COX-2 inhibitors (Muller and Schwarz, 2008) and the TNF antagonist, infliximab (Raison et al., 2013), medications with neuroprotective properties (e.g., antidepressants, mood stabilisers) (Dodd et al., 2013; Lee et al., 2012; Malhi et al., 2012), herbs and nutrients with anti-inflammatory and antioxidant properties (e.g., curcumin, resveratrol, omega-3 fatty acids, green tea, n-acetyl cysteine, CoQ10, selenium, zinc, alpha lipoic acid and vitamins such as A, C and E) (Alappat and Awad, 2010; Floyd, 1999; Kim et al., 2008; Lopresti et al., 2012; Magalhaes et al., 2011; Scapagnini et al., 2012) and lifestyle changes known to enhance neurogenesis (e.g., sleep hygiene interventions, meditation, yoga, relaxation therapies and exercise) (Doraiswamy and Xiong, 2007; Kiecolt-Glaser et al., 2010; Lopresti et al., 2013).

10. *What effect do psychotropic medications have on weight gain, overall health status and relevant biomarker changes in psychiatric patients?*

    As discussed previously, a significant problem associated with many psychiatric medications is weight gain. This is a serious issue for many patients who often cite this as a major reason for their discontinued drug use (Serretti and Mandelli, 2010). As proposed in Figure 3, drug-induced weight gain may potentially contribute to worsening mental health through both physiological and psychological effects associated with increased

adiposity. Weight loss interventions and the prevention of weight gain may therefore be especially germane for such patients as it could lead to enhanced medication compliance and improved treatment outcomes.

Although weight gain is linked with several psychiatric medications, part of this weight gain may also be due to the psychiatric illness. This overlooked area requires consideration in future studies on weight gain, obesity and psychiatric disorders.

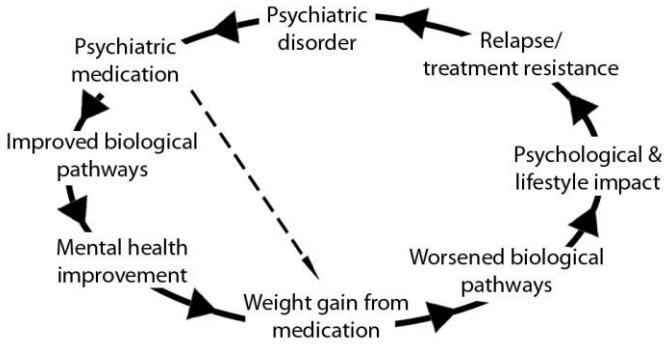

Figure 3. *The problem of medication-induced weight gain in psychiatric disorders.* A significant problem associated with many psychiatric medications is weight gain. While medications may lead to mental health improvements for some patients, weight gain can have detrimental effects on several biological pathways (e.g., inflammation, oxidative stress, HPA imbalances, neuroprogression, HPA axis imbalances, mitochondrial disturbances). Weight gain may also contribute to changes in lifestyle, self-concept and other psychological processes that can further compound problems associated with psychiatric disorders. The end result is relapse or treatment resistance. (The dotted arrow represents patients who do not benefit from psychiatric medication)

While only preliminary, alpha lipoic acid (a potent antioxidant) holds some promise as an effective agent in preventing antipsychotic-induced weight gain in patients with schizophrenia (Kim et al., 2008; Ratliff et al., 2013). The medications metformin, d-fenfluramine, sibutramine, topiramate, and reboxetine were also confirmed in a recent meta-analysis to attenuate antipsychotic-related weight gain (Maayan et al., 2010). While these findings are positive, the effects of these medications on mental health outcomes and inflammatory and metabolic parameters in psychiatric patients require further investigation.

While our understanding of the relationship between obesity and psychiatric disorders is expanding, it is evident from this review that there are significant gaps in research. The dangers of obesity and the importance of weight loss are often discussed in relation to chronic illnesses such as diabetes and cardiovascular disease. However, their importance in mental health prevention and treatment should also be recognised.

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Adrian Lopresti conducted a literature search and wrote the first draft of this manuscript. Peter Drummond reviewed the manuscript and provided feedback, corrections and recommendations on further drafts of this manuscript. All authors contributed to and have approved the final manuscript.

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Chapter Summary

As detailed in this chapter, several lifestyle factors are associated with major depressive disorder. While these lifestyle-related behaviours influence psychological and social elements important in major depression, they also impact on the reviewed depressogenic biological pathways. It is these multiple lifestyle influences that contribute to the complexities associated with the prevention and treatment of major depression. Further compounding difficulties are the onset of depressive symptoms (e.g., fatigue, poor sleep, and anhedonia) that often promote negative lifestyle changes that exacerbate the severity of depressive symptoms.

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Chapter 4:
Psychological and pharmaceutical interventions and their influence on biological mechanisms associated with major depression

While lifestyle factors can influence the previously mentioned dysregulated pathways, there is evidence that antidepressant medications and psychological therapies also play a significant role. In a meta-analysis by Hannestad and colleagues (2011) it was concluded that antidepressant medications, particularly SSRIs, were associated with reductions in IL-6 and IL-1β. There is also evidence that antidepressant medications can increase antioxidant status and decrease markers of oxidative stress both in animal- (Abdel-Wahab and Salama, 2011; Battal et al., 2014) and human-based studies (Bilici et al., 2001; Herken et al., 2007; Khanzode et al., 2003; Kotan et al., 2011). Although findings are mixed, in a systematic review and meta-analysis on 1504 subjects it was confirmed that BDNF levels increased significantly after antidepressant treatment (effect size 0.62). In addition, there were significant correlations between changes in BDNF concentrations and changes in depression scores (Brunoni et al., 2008). Chronic antidepressant treatment also promotes adult hippocampal neurogenesis, synaptogenesis and neuronal maturation (Lee and Kim, 2010; Neto et al., 2011). Antidepressants also influence HPA activity through their effect on mineralocorticoid and glucocorticoid receptors (Mason and Pariante, 2006) and their normalising effects on cortisol concentrations (Dziurkowska et al., 2013; Hinkelmann et al., 2012). It is likely that a combination of these mechanisms of change at least partly accounts for the relatively slow symptom-relieving effects of antidepressant medications, despite their rapid influence on monoamine activity.

There are findings from several studies confirming that participation in CBT influences many of the depressogenic biological pathways. For example, women with first-episode depression experienced reductions in IL-6 after seven sessions of CBT (Gazal et al., 2013). CBT offered to depressed women following coronary artery bypass graft surgery was accompanied by improvements in natural killer cell cytotoxicity and decreased IL-6, CRP, and postoperative infectious illnesses (Doering et al., 2007). In a further study on depressed patients, participation in CBT was associated with reductions in Toll-like receptor-4 signalling, with larger reductions in pro-inflammatory markers associated with greater clinical improvements (Keri et al., 2014). CBT is also accompanied by reductions in cortisol concentrations. For example, CBT was associated with cortisol reductions in women with functional hypothalamic amenorrhea (Michopoulos et al., 2013) and in caregivers of Alzheimer's patients (Aboulafia-Brakha et al., 2014). CBT applied in a forest environment is especially accompanied by lowered cortisol concentrations in people with major depressive disorder (Kim et al., 2009) and elderly patients with hypertension (Sung et al., 2012).

In relation to other psychological and relaxation-based interventions, reductions in hyperglycaemic- and exercise-induced oxidative stress have been demonstrated following a period of diaphragmatic breathing (Martarelli et al., 2011a; Martarelli et al., 2011b). Six months of yoga practice in healthy male volunteers elevated concentrations of glutathione and increased total antioxidant status (Sinha et al., 2007). Meditation practice also influences inflammatory pathways by lowering neurogenic inflammation (Rosenkranz et al., 2013) and cortisol concentrations (Bottaccioli et al., 2014; Turakitwanakan et al., 2013). Meditation practice may also positively influence brain plasticity (Xiong and Doraiswamy, 2009), with time spent engaging in mindful-attention training positively correlating with hippocampal volume (Desbordes et al., 2014).

Despite the positive influence of psychological and pharmacological interventions on several biological pathways, it has been demonstrated that baseline disturbances in some of these pathways are associated with a poorer response to treatment. For example, people with chronic fatigue syndrome and low cortisol levels experienced a poorer response to CBT, reflected by minimal changes in fatigue, disability and psychiatric symptoms (Roberts et al., 2010). Among older adults with depression, higher daily outputs of cortisol and flatter diurnal slopes were associated with minimal improvements in depressive symptoms following CBT (Holland et al., 2013). A poorer treatment response from CBT and interpersonal therapy also occurred in depressed patients with elevated levels of baseline CRP (Harley et al., 2010). In relation to antidepressant treatments, elevated cytokine concentrations of IL-6, TNFα and IL-1 receptor antagonist were associated with lowered treatment efficacy from antidepressant medications (Eller et al., 2008; Lanquillon et al., 2000; Maes et al., 1997; O'Brien et al., 2007). Lower baseline vascular endothelial growth factor and monocyte chemoattractant protein-1 is also accompanied by a reduced response to antidepressant medications (Carvalho et al., 2013). These findings indicate that inflammatory-related factors lower the efficacy of pharmaceutical and psychological treatments. Therefore, more comprehensive interventions possibly comprising a combination of antidepressant and psychological therapy, and/or the addition of nutraceutical and lifestyle-based interventions, may be necessary for such individuals.

Summary

While research is still preliminary, it seems that psychological and pharmaceutical treatments for depression are associated with positive influences on several depressogenic biological pathways. However, further research is certainly required, particularly in the area of psychological treatments. What is noteworthy are findings of treatment resistance associated with significant baseline dysregulations in some of these biological pathways, particularly those associated with immuno-inflammation and HPA activity. Greater

understanding of the relevance of these findings is required, with the need for stronger controls for lifestyle and physical-related factors that are often associated with these biological disturbances.

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Chapter 5:
An examination of curcumin for the treatment of major depression

In addition to the more consistently utilised pharmacological and psychological interventions, certain nutraceuticals may also influence pathways associated with major depression. Curcumin, derived from the Indian spice turmeric, is one agent that has been demonstrated through *in vitro* and *in vivo* studies to influence all of these depressogenic pathways and therefore has the potential to be an effective treatment for major depressive disorder (Lopresti et al., 2012). In this chapter, two published papers are included. The first is a review of *in vitro* and *in vivo* studies examining the effects of curcumin on depressogenic biological pathways. It was the findings from this review that led to the hypothesis that curcumin may be an effective agent for the treatment of major depression. This was subsequently investigated in a randomised, double-blind, placebo controlled study, and details are included in the second published paper.

Multiple antidepressant potential modes of action of curcumin: A review of its anti-inflammatory, antioxidant, immune-modulating and neuroprotective effects

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Abstract

Curcumin is the principal curcuminoid of the popular Indian spice turmeric and has attracted increasing attention for the treatment of a range of conditions. Research into its potential as a treatment for depression is still in its infancy, although several potential antidepressant mechanisms of action have been identified. Research completed to date on the multiple effects of curcumin is reviewed in this paper, with a specific emphasis on the biological systems that are compromised in depression. The antidepressant effects of curcumin in animal models of depression are summarised, and its influence on neurotransmitters such as serotonin and dopamine is detailed. The effects of curcumin in moderating hypothalamus-pituitary-adrenal (HPA) disturbances, lowering inflammation, and protecting against oxidative stress, mitochondrial damage, neuroprogression and intestinal hyperpermeability, all of which are compromised in major depressive disorder, are also summarised. With increasing interest in natural treatments for depression, and efforts to enhance current treatment outcomes, curcumin is presented as a promising novel, adjunctive or stand-alone natural antidepressant.

Major depression is one of the most common psychiatric disorders in the Western World and is the leading cause of disability (as measured by years lived with a disability). In the year 2000 it was the 4th leading contributor to the global burden of disease and by the year 2020 is projected to be second only to ischemic heart disease in the amount of disability experienced by sufferers (WHO, 2008).

Major depression is a heterogeneous disorder recognised as having a complex and multifactorial aetiology originating from the interaction between environmental and genetic factors. As depicted in figure 1, these lead to a range of disturbances including: neurotransmitter imbalances associated with lowered serotonin, dopamine and noradrenaline, and increased glutamate activity; HPA disturbances typically characterised by increased HPA activity and glucocorticoid resistance; dysregulated inflammatory pathways as evidenced by increased levels of proinflammatory cytokines, acute phase proteins and kynurenine pathway metabolites; increased oxidative and nitrosative damage associated with reduced antioxidant defences; neuroprogression resulting in neurodegeneration, apoptosis, reduced neurogenesis and neuronal plasticity; and mitochondrial disturbances in the form of increased damage to mitochondria and mitochondrial DNA, and lowered ATP production. (Leonard and Maes, 2012; Maes et al., 2009c; Manji et al., 2001; Raison and Miller, 2011). It is these multiple pathways that make the effective treatment of depression difficult, with current therapies achieving far from optimal remission rates of between 20 to 40 percent (Warden et al., 2007). This has motivated a search for alternative pharmacological, psychological, environmental, and even nutraceutical treatment options to enhance current treatment outcomes.

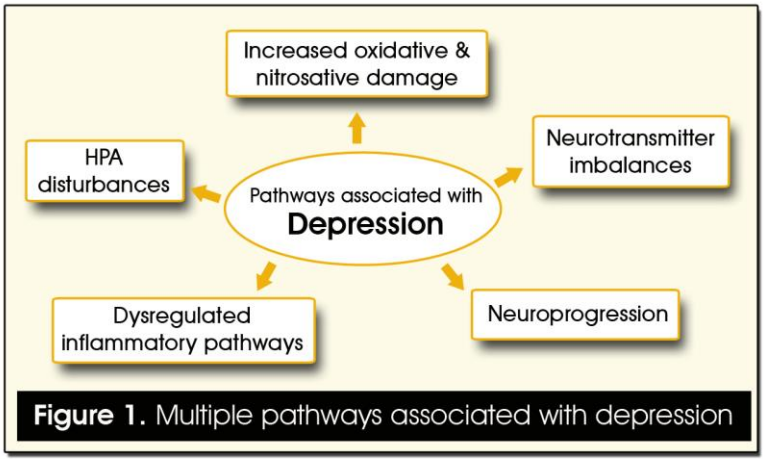

Figure 1. Multiple pathways associated with depression

Given the multifactorial nature of depression, an enhancement of treatment efficacy is likely to occur from therapies that target multiple mechanisms. This is likely to be achieved by combining therapies and/or utilising treatments with multiple mechanisms of action. Curcumin, derived from the spice turmeric, is a potential natural substance that may at least partly fulfil this criterion. As demonstrated in figure 2, curcumin has been shown to have a large array of molecular targets of action which may prove to be beneficial for the treatment and prevention of depression and other diseases (Aggarwal and Sung, 2009; Gupta et al., 2012). This has already led to two published brief reviews highlighting the potential antidepressant effects of curcumin (Kulkarni et al., 2009; Kulkarni and Dhir, 2010).

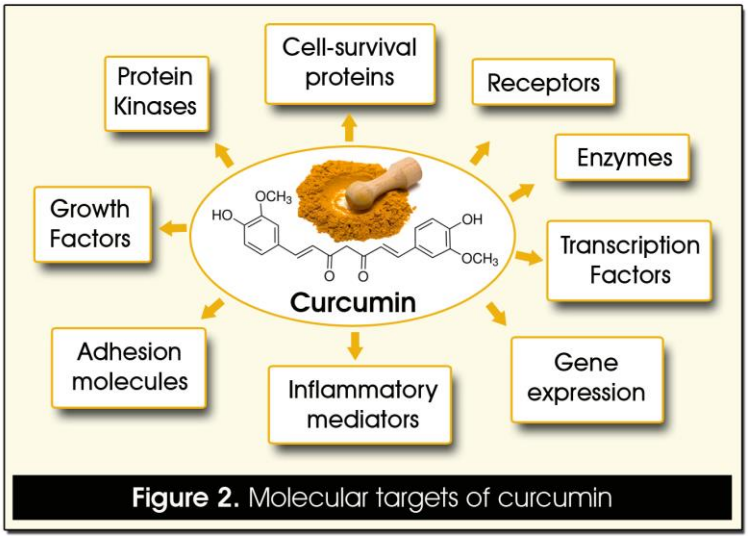

Figure 2. Molecular targets of curcumin

Interest in the benefits of curcumin has increased dramatically over the past decade with a number of clinical studies currently underway investigating its efficacy for treating and preventing a range of diseases including certain cancers (e.g., http://clinicaltrials.gov/ct2/show/NCT00094445) , Alzheimer's disease (e.g., http://www.anzctr.org.au/trial_view.aspx?id=336793) and musculoskeletal conditions (e.g., http://clinicaltrials.gov/ct2/show/NCT00752154)In addition, at least one unpublished study has been completed investigating the antidepressant effects of curcumin (http://clinicaltrials.gov/ct2/show/NCT01022632), although the outcomes of this study have not yet been released. The research completed to date on the multiple effects of curcumin is reviewed in this paper, with a specific emphasis on the biological systems that are compromised in depression. The antidepressant effects of curcumin in animal models of depression is summarised, and its effect on neurotransmitters, HPA disturbances, inflammation, oxidative stress, mitochondria, neuroprogression and intestinal hyperpermeability, all of which are disturbed in depression, are detailed.

Animal behavioural models of depression

Despite the fact that no animal model is able to incorporate all aspects of depressive symptoms in humans, the forced swimming test (FST) is a reliable and valid tool for screening the antidepressant effects of drugs (Petit-Demouliere et al., 2005). Animals (typically rats and mice) are subjected to two trials where they are forced to swim in an inescapable cylinder filled with water. The time animals spend immobile in the second trial provides a measure of despair, and has been shown to be reduced by antidepressant drugs (Petit-Demouliere et al., 2005).

The tail suspension test (TST) is another animal model of depression that has good reliability and predictive validity (Cryan et al., 2005). In the TST, animals are subjected to the

short-term, inescapable stress of being suspended by their tail, with time spent in an immobile posture providing a measure of depressive behaviour. Various antidepressant medications have been shown to reverse immobility and to promote escape-related behaviour (Steru et al., 1985).

Antidepressant effects of curcumin in animal models

The antidepressant effects of curcumin have been evaluated through the FST and TST in over a dozen studies in the past decade. These have consistently demonstrated that both acute (Arora et al., 2011; Chimakurthy and Talasila, 2010; Gilhotra and Dhingra, 2010; Kulkarni et al., 2008; Sanmukhani et al., 2011; Wang et al., 2008) and chronic (Bhutani et al., 2009; Huang et al., 2011; Li et al., 2009; Sanmukhani et al., 2011; Xia et al., 2007; Xu et al., 2005b) administration of curcumin to rats and mice reduces immobility time.

For example, both in the acute models of FST and TST, and the chronic model of FST with a water wheel, curcumin had significant antidepressant-like activity compared with a vehicle control. The effects of curcumin were similar to that of fluoxetine and imipramine although when administered in combination, antidepressant effects were not enhanced (Sanmukhani et al., 2011). Similar results have been found in other animal models of depression, with curcumin having similar antidepressant efficacy to fluoxetine (Li et al., 2009; Wang et al., 2008).

Bilateral olfactory bulbectomy in rats causes changes in behaviour, and in the endocrine, immune and neurotransmitter systems, that lead to many characteristics seen in patients with major depression. Bulbectomy is believed to cause major dysfunction in the cortical-hippocampal-amygdala circuit similar to that seen in people suffering from major depression (Song and Leonard, 2005). Chronic, but not acute administration of antidepressants corrects most of the changes evoked by bulbectomy (Song and Leonard, 2005). A study assessing the

effects of curcumin demonstrated that its chronic administration was also able to reduce immobility time and reverse the behavioural abnormalities induced by bulbectomy (Xu et al., 2005a).

By depleting monoamines and increasing oxidative stress, reserpine is a drug that increases pain and depressive symptoms. An investigation into the protective effects of curcumin on the reserpine-induced pain-depression dyad in rats demonstrated that curcumin was effective in ameliorating a number of behavioural changes induced by reserpine (Arora et al., 2011). Finally, depressive-like behaviours characterised by a decrease in sugar consumption and an increase in immobility time were induced by 3 weeks of corticosterone injections in rats. Concurrent treatment with curcumin reduced depressive-like behaviours, demonstrated by a 46% increase in sucrose consumption and a 57% reduction in immobility time compared with rats receiving corticosterone injections alone (Huang et al., 2011).

Based on the studies reviewed, in animal models of depression, oral and intraperitoneal curcumin appear to have potent antidepressant properties with effects similar to antidepressants such as the serotonin reuptake inhibitor fluoxetine and the tricyclic imipramine.

Depression and immuno-inflammation

Interest in the association between major depression and inflammation was triggered by studies demonstrating increased levels of inflammatory mediators in depression. This led to the development of inflammatory models of depression and prompted initial comparisons between the symptoms of depression and 'sickness behaviours' such as anorexia, soporific effects, reduction of locomotor activity and exploration, anhedonia and cognitive disturbances (Dantzer et al., 2011; Raison et al., 2006). These were later confirmed to be distinct conditions,

with sickness behaviour an adaptive, acute state, whereas depression is a disabling, progressive disorder (Maes et al., 2012a)

Three recent meta-analyses have all confirmed that depression is associated with elevated levels of pro-inflammatory cytokines and other inflammatory mediators. Howren et al. (2009) concluded that depression in clinic and community samples was associated with high levels of C-reactive protein (CRP), interleukin-1 (IL-1), and interleukin-6 (IL-6). In a meta-analysis by Dowlati et al. (2010), levels of tumour necrosis factor-α (TNF-α) and IL-6 were significantly higher in depressed patients than controls. Finally, a meta-analysis by Liu et al. (2012) demonstrated that the blood levels of soluble interleukin-2 receptors (sIL-2R), TNF-α and IL-6 were all significantly higher in patients with major depressive disorder than in controls. There is also evidence that major depression is characterised by a Th-1-like cell-mediated response, as evidenced by increased production of interferon-γ (IFN-γ), increased IFN-γ/IL-4 ratios and increased neopterin levels (Maes et al., 1994; Myint et al., 2005).

Further support for the relationship between depression and inflammation is provided by a meta-analysis on the anti-inflammatory effects of antidepressant medications, which concluded that antidepressants reduced levels of cytokines IL-1β and possibly IL-6, but not TNF-α (Hannestad et al., 2011b). The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine, which has rapid antidepressant effects in treatment-resistant patients with major depressive disorder, also has anti-inflammatory effects (Loix et al., 2011; Mathew et al., 2012)

While increased inflammation is not found in all patients with depression, it is argued that its effects may be relevant to a subset of patients (Raison and Miller, 2011). Researchers have also become increasingly interested in the impact of inflammation on kynurenine pathway metabolites which have both neurotoxic and neuroprotective qualities (Dantzer et al., 2011; Maes et al., 2011c).

Immuno-inflammatory effects of curcumin

Effects of curcumin on inflammatory pathways

Extensive research using a wide range of *in vitro* models has indicated that curcumin can reduce the inflammatory response by regulating the production of a range of inflammatory molecules (Basnet and Skalko-Basnet, 2011; Srivastava et al., 2011). Research performed in animals also provides strong evidence for the beneficial effects of curcumin in various diseases associated with inflammation including inflammatory bowel disease, obesity, cardiovascular disease and certain cancers (Gupta et al., 2012).

Evidence of anti-inflammatory effects in human studies is accumulating and has so far been promising. For example, in a clinical trial on osteoarthritis patients, the administration of a patented form of curcumin (Meriva®) significantly reduced a number of inflammatory markers including IL-1β, IL-6, and the erythrocyte sedimentation rate (ESR) (Belcaro et al., 2010). In another randomised clinical trial, curcumin (BCM-95®) given to patients with rheumatoid arthritis significantly reduced the ESR to levels similar to that obtained from the non-steroidal anti-inflammatory drug, diclofenac sodium (Chandran and Goel, 2012). Further evidence of the anti-inflammatory effects of curcumin was demonstrated in a randomised, double-blind, placebo-controlled study on patients with overt type 2 diabetic nephropathy where curcumin administration reduced serum levels of TGF-β and IL-8, and urinary IL-8 (Khajehdehi et al., 2011). Finally, in another study on patients with type 2 diabetes, curcumin lowered levels of IL-6 and TNF-α significantly more than placebo (Usharani et al., 2008).

COX-2 selective inhibitors are a form of non-steroidal anti-inflammatory drug (NSAID) that directly targets COX-2, an enzyme responsible for the production of prostaglandin E_2 (PGE_2). PGE_2 is a pro-inflammatory chemical messenger involved in pain, fever and swelling. In normal conditions, COX-2 is not expressed in most cells, but elevated levels are found

during inflammation which, in turn, stimulates the production of PGE_2. As a co-factor, COX-2 is associated with the increased expression of IDO (Basu et al., 2006; Cesario et al., 2011; Lee et al., 2009) and with inflammatory cytokines (Abbasi et al., 2012).

Studies in the area of depression have provided evidence of increased PGE_2 production and COX-2 expression in depressed people. For example, increased concentrations of PGE_2 in the saliva of patients with major depressive disorder were identified (Ohishi et al., 1988). Moreover, increased levels of PGE_2 were reported both in the CSF and serum of depressed patients (Calabrese et al., 1986; Linnoila et al., 1983). Increased expression of the genes encoding for COX-2 were also found in the peripheral blood cells of patients with recurrent depression (Galecki et al., 2012). The antidepressants fluoxetine and amitriptyline also inhibit cytokine-induced PGE_2 production by inflammatory cells (Yaron et al., 1999). Recent interest in the potential of COX-2 inhibitors to augment antidepressant therapies also show promise, with a number of positive findings from animal models of depression and from preliminary human clinical trials (Muller and Schwarz, 2008).

In a six-week double-blind, placebo-controlled trial, depressed patients treated with a combination of fluoxetine and the COX-2 inhibitor, celecoxib, experienced greater improvement in mood compared with those treated with a combination of fluoxetine and placebo (Akhondzadeh et al., 2009). In a double-blind, add-on study using the noradrenergic reuptake inhibitor reboxetine as the antidepressant, Muller et al. (2006) obtained a similar outcome. The combination of reboxetine and celecoxib led to significantly greater improvements compared with the reboxetine-alone treated group. Also, in an open-label pilot study, the mixed COX-1/COX-2 inhibitor acetylsalicylic acid accelerated the antidepressant effect of fluoxetine and increased the response rate in depressed non-responders to fluoxetine (Mendlewicz et al., 2006). More recently, celecoxib enhanced the efficacy of the serotonergic

antidepressant sertraline in 40 depressed patients. Patients in the celecoxib and sertraline group experienced a significantly greater response (95%) and remission (35%) rate compared with those receiving placebo and sertraline (50% response and 5% remission) (Abbasi et al., 2012).

Investigation into the biological activities of curcumin have demonstrated that it can down-regulate COX-2 expression and PGE_2 synthesis (Hong et al., 2004; Lee et al., 2011; Moriyuki et al., 2010; Plummer et al., 1999), therefore providing an alternative natural option as a COX-2 inhibitor. While further human clinical studies are required in this area, the promising antidepressant findings of pharmaceutical COX-2 inhibitors provides another potential mechanism of action of for the antidepressant effect of curcumin.

Effects of curcumin on immune pathways

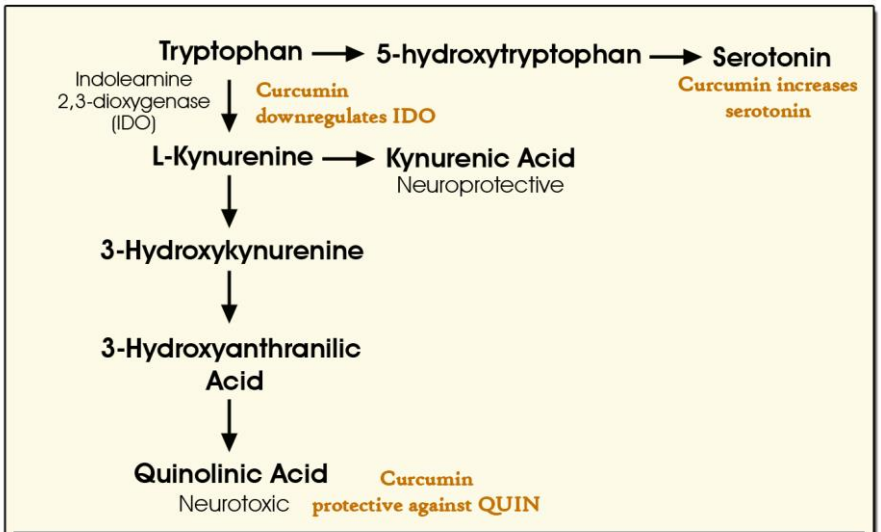

Figure 3. Kynurenine pathway and its metabolites.

The kynurenine pathway starts with the degradation of tryptophan by the enzyme, indoleamine 2,3-dioxygenase (IDO) which is upregulated by pro-inflammatory cytokines (e.g. IFN-γ, TNF-α, IL-, IL-6). Curcumin has the potential to reduce the expression of IDO and is neuroprotective against the excitotoxic effects of quinolinic acid (QUIN). Curcumin also increases serotonin levels, possibly through it effect on IDO, monoamine oxidase and serotonin receptors.

IDO is an enzyme expressed in multiple cell types including macrophages, dendritic cells, astrocytes and microglia and is strongly activated by the pro-inflammatory cytokine IFN-γ and to a lesser extent TNF-α, IL-1, and IL-6. IDO can also be induced by lipopolysaccharides

(LPS) (Chen and Guillemin, 2009; Stone et al., 2012). As shown in Figure 3, IDO is important in depression as it reduces serotonin synthesis by catabolising tryptophan, the primary amino-acid precursor of serotonin, into kynurenine pathway metabolites. The role of serotonin in depression is already well recognised; however, accumulating research shows that a number of kynurenine pathway metabolites can impact on several mechanisms associated with depression (Maes et al., 2011c; Maes et al., 2007). For example, excess levels of the NMDA agonist and kynurenine pathway metabolite, quinolinic acid (QUIN), are excitotoxic, leading to degenerative changes in the central nervous system. It can increase the generation of free radicals and induce lipid peroxidation. The damaging effects of QUIN can also contribute to mitochondrial degeneration and in experimental models QUIN has anxiogenic effects (Stone et al., 2012). Excess QUIN levels were found in depression (Raison et al., 2010; Steiner et al., 2011), and in neurological conditions such as Alzheimer's disease, Parkinson's disease and multiple sclerosis (Kincses et al., 2010; Zádori et al., 2009).

Another kynurenine pathway metabolite and NMDA antagonist, kynurenic acid (KYNA), is considered neuroprotective and inversely regulates dopaminergic activity. Its balance with QUIN is important as it is considered protective against the excitotoxicity of QUIN (Myint, 2012). KYNA levels were found to be low in depression (Maes et al., 2011b; Myint et al., 2007) and, more recently, were observed to be particularly low in patients with somatization (Maes et al., 2011b; Maes and Rief, 2012). KYNA levels were also associated with an increased risk of depression in people undergoing IFN-α treatment for hepatitis C virus (Wichers et al., 2005).

Research into the effects of curcumin on IDO expression is only preliminary. However, studies identified to date have been positive. One study demonstrated that curcumin significantly inhibited the expression and activity of IDO in IFN-γ-stimulated bone marrow dendritic mice cells (Jeong et al., 2009). In a study on cancer cells induced by IFN-γ, curcumin

was also reported to inhibit the expression of IDO (Zhang et al., 2008). Finally, in an *in vitro* and *in vivo* investigation, curcumin delivered to mice significantly attenuated LPS-induced increases in IDO expression in bone marrow-derived dendritic cells (Jung et al., 2010).

Further evidence of curcumin's immuno-modulating effects are demonstrated by its ability to lower Th-17 autoimmune responses (Kanakasabai et al., 2012; Xie et al., 2009) which have recently been shown to be upregulated in major depression (Chen et al., 2011). Curcumin also decreases the expression of Th-1 cytokines (e.g., IFN-γ, TNF-α) and increases the expression of Th-2 cytokines (e.g., IL-4 and IL-10) (Bereswill et al., 2010; Zhang et al., 2006). This may prove to be beneficial for the treatment of depression given consistent findings of increased Th-1-like cell-mediated responses in major depression (Maes, 2011; Maes et al., 1994; Myint et al., 2005).

Several studies have also investigated the influence of curcumin on the lipopolysaccharide (LPS)-induced immune response. One such study revealed that the systemic administration of LPS to rabbits increased core temperature and hypothalamic levels of glutamate and hydroxyl radicals along with increased plasma levels of TNF-α, IL-1β, and IL-6. Pre-treatment with curcumin one hour before an intravenous dose of LPS significantly reduced the LPS-induced overproduction of circulating TNF-α, IL-1β, and IL-6, and brain glutamate, PGE2, and hydroxyl radicals (Huang et al., 2008).

Depression and neurotransmitters

The monoamine-deficiency theory is the most recognised and investigated causative model of major depression. It is postulated as the primary mechanism of action of popular pharmaceutical antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs), is to increase the availability of monoamines such as serotonin, noradrenaline (i.e., norepinephrine) and, possibly, dopamine.

According to this theory, the underlying pathophysiological basis of depression is a depletion of these neurotransmitters in the central nervous system (Maletic et al., 2007).

Serotonin is the most extensively studied neurotransmitter in depression, with evidence of its deficiency emerging from studies using tryptophan depletion (which reduces central serotonin synthesis) (Toker et al., 2010), studies demonstrating abnormalities in serotonin receptors in depressed patients (Carr and Lucki, 2011), research showing increased availability of monoamine oxidase, an enzyme that metabolises serotonin and other monoamines in the brain of depressed people (Meyer et al., 2006), and evidence of abnormalities in the expression of the enzyme tryptophan hydroxylase, which is involved in serotonin synthesis (Matthes et al., 2010). The monoaminergic theory has prompted research into the potential of curcumin in altering neurotransmitters such as serotonin, dopamine and noradrenaline. A selection of these studies is reviewed.

Effects of curcumin on serotonin, dopamine and noradrenaline

Both animal and *in vitro* studies conducted over the past decade have now confirmed that curcumin is able to influence levels of serotonin, dopamine and noradrenaline in the central nervous system. For example, in a chronic unpredictable mild stress (CUMS) model with rats, curcumin reduced serum corticosterone levels and attenuated CUMS-induced reductions of serotonin (Li et al., 2009). Curcumin administered to mice for 21 days prior to the FST was also shown to markedly attenuate FST-induced decreases in concentration of serotonin, the serotonin metabolite 5-hydroxyindoleacetic acid, noradrenaline and dopamine, as well as increases in serotonin turnover (Xia et al., 2007). Similar results were found following the acute administration of curcumin to mice one hour prior to the FST. Curcumin dose-dependently increased serotonin, and at higher doses increased dopamine levels. However, no changes in noradrenaline levels were found. The researchers demonstrated that curcumin

was able to inhibit the monoamine oxidase enzymes (both MAO-A, and at higher doses MAO-B) and when co-administered with piperine, a bioavailability enhancing agent, the effects of curcumin on pharmacological, biochemical, and neurochemical activities were potentiated (Kulkarni et al., 2008). Similar findings were obtained when rats were subjected to chronic unpredictable stress. Curcumin treatment for 21 days significantly reversed the chronic unpredictable stress-induced behavioural (increase in immobility period), biochemical (increase in monoamine oxidase activity) and neurochemical (depletion of brain monoamine levels, except noradrenaline) alterations. The combination of piperine with curcumin again showed significant potentiation of its anti-immobility, neurotransmitter enhancing (serotonin and dopamine) and MAO-A effects compared to curcumin administration alone (Bhutani et al., 2009).

In an animal study on the effects of curcumin on serotonin (5-HT) receptors, the antidepressant-like effects of curcumin in the FST were related to the serotonergic system, possibly due to an interaction with 5-$HT_{1A/1B}$ and 5-HT_{2C} receptors (Wang et al., 2008). Further evidence of the monoamine effects of curcumin has been demonstrated in rats submitted to a bilateral olfactory bulbectomy. The administration of curcumin completely reversed induced reductions in serotonin and noradrenaline in the hippocampus and frontal cortex (Xu et al., 2005a). Curcumin also reversed reseperine-induced reductions in dopamine, noradrenaline and serotonin in rats (Arora et al., 2011). Pre-treatment with curcumin reversed haloperidol-induced reductions of dopamine, noradrenaline and serotonin in rats (Bishnoi et al., 2008). In a follow-up study, the co-administration of piperine significantly enhanced the effect of curcumin on these monoamines (Bishnoi et al., 2011).

Collectively, these animal studies provide strong support for the monoaminergic effects of curcumin. Curcumin enhances levels of serotonin and dopamine and, to a lesser extent,

noradrenaline, following exposure to acute and chronic stress. The studies reviewed in this section indicate that curcumin has an inhibitory effect on monoamine oxidase and influences 5-$HT_{1A/1B}$ and 5-HT_{2C} receptors, all of which play a role in depression.

Effects of curcumin on glutamate

Glutamate is the major excitatory synaptic neurotransmitter in the central nervous system and plays a vital role in the regulation of synaptic plasticity, learning, and memory (McEntee and Crook, 1993). Increasing research has demonstrated altered levels of glutamate in plasma, cerebrospinal fluid (CSF) and various areas of the brain in people with depression. An increasing number of reports also suggest potential antidepressant effects of anti-glutamatergic agents, such as ketamine, amantadine, and riluzole (Gao and Bao, 2011; McNally et al., 2008).

Curcumin inhibited the release of glutamate evoked by exposing synaptosomes to the K^+ channel blocker 4-aminopyridine (4-AP) (Lin et al., 2011). Because the inhibitory effect of curcumin on glutamate release was completely abolished by the antidepressant fluoxetine, it was concluded that these two substances may use a common intracellular mechanism to inhibit glutamate release from rat prefrontal cortex nerve terminals. When the effects of curcumin and fluoxetine were compared, curcumin had significantly greater inhibitory effects on glutamate release than fluoxetine (Lin et al., 2011).

Depression and HPA disturbances

The hypothalamic, pituitary and adrenal (HPA) axis plays a significant role in the body's stress response and is initiated by the secretion of corticotrophin releasing hormone (CRH) and arginine-vasopressin (AVP) from the hypothalamus. This, in turn, activates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, which then stimulates the

secretion of glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal cortex. These glucocorticoids impact on their receptors and are involved in the negative feedback control of CRH and AVP release from the hypothalamus (Zunszain et al., 2011).

Abnormalities in the activity of the HPA axis have long been observed in major depression (Pariante and Lightman, 2008). This has been characterised by heightened cortisol secretion in patients presenting with melancholic depression, and reduced levels in people presenting with atypical depression (Gold and Chrousos, 2002). Increasing research has also demonstrated that depression is associated with a hypersecretion of CRH and impairment in the responsiveness to glucocorticoids, a phenomenon known as glucocorticoid resistance (Pariante and Lightman, 2008). Depression is also associated with an increased size and activity of the pituitary and adrenal glands (Nemeroff et al., 1992).

Effects of curcumin on HPA disturbances

A few studies have examined the effect of curcumin in regulating HPA disturbances, namely its effect in moderating the hypersecretion of corticosterone and subsequent neuroprotection. For example, rats subjected to 3 weeks of corticosterone injections exhibited depressive-like behaviours, as demonstrated by a significant decrease in sucrose consumption and an increase in immobility time in the FST. These behaviours were significantly reduced in those rats treated concurrently with curcumin (Huang et al., 2011). In a study on rats exposed to 4 weeks of chronic unpredictable mild stress, curcumin was able to moderate increases in serum corticosterone at levels similar to those obtained by fluoxetine (Li et al., 2009). In a final study, exposure of corticosterone to rat neurons decreased mRNA levels for three serotonin receptor subtypes, 5-HT_{1A}, 5-HT_{2A} and 5-HT_{4}. Pre-treatment with curcumin one hour prior to corticosterone exposure reversed this effect on 5-HT_{1A} and 5-HT_{4} receptors, but not for the 5-

HT_{2A} receptor. Moreover, curcumin significantly reduced neuronal loss, indicating that it could protect cells from corticosterone-induced toxicity. Curcumin also inhibited corticosterone-induced morphological changes such as increases in soma size, dendritic branching and dendritic spine density, and elevated synaptophysin expression in cortical neurons. The antidepressant fluoxetine also provided a protective effect against the toxicity of corticosterone and reversed corticosterone-induced down-regulation of mRNA levels for three receptors: 5-HT_{1A}, 5-HT_{2A} and 5-HT_4 (Xu et al., 2011).

In sum, these studies highlight the potential protective effects of curcumin on stress-induced cortisol production. HPA imbalances in depression may prove to be at least partly ameliorated by curcumin, although further studies are required.

Depression and neuroprogression

Neurogenesis is the process by which new neurons are formed from populations of neural stem or progenitor cells residing in discrete regions of the CNS (Abdipranoto et al., 2008). Recent research into neuroanatomy and neurochemistry has increasingly demonstrated that major depression is associated with impaired neurogenesis, neuronal plasticity, and subsequent neurodegeneration. This is indicated by stress-induced alterations to the number and shape of neurons and glia in the brain regions of depressed patients (Duman, 2009). Depression is also associated with a decrease in proliferation of neural stem cells (Eyre and Baune, 2012).

Neuronal plasticity is influenced by a range of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which is the most abundant and widely distributed neurotrophin in the central nervous system (Martinowich and Lu, 2008). BDNF plays a role in regulating a large array of functions including neuronal survival, growth and proliferation, and levels usually are low in people suffering from major depression (Duman, 2009; Lee and Kim, 2010).

Chronic administration of several classes of antidepressants, including monoamine oxidase inhibitors, SSRIs, tricyclic agents, and SNRIs increases BDNF levels (Duman and Monteggia, 2006; Sen et al., 2008). The detrimental effects of early life and chronic stress on BDNF, and evidence of increased levels of BDNF following physical exercise and electroconvulsive therapy, provides further support for a role of BDNF in the pathogenesis of depression (Martinowich et al., 2007; Nagahara and Tuszynski, 2011).

Neuroprotective effects of curcumin

Preliminary investigations into the neuroprotective effective of curcumin have provided evidence of its ability to enhance BDNF and attenuate stress-induced neurodegeneration. Repeated corticosterone injections were shown to significantly decrease BDNF levels in the hippocampus and frontal cortex of rats, which curcumin was able to significantly ameliorate (Huang et al., 2011). In another study, rats exposed to a range of daily stressors over a 20-day period were administered either 3 doses of curcumin orally or the antidepressant imipramine. Curcumin administration at higher doses reversed the stress-induced decrease in hippocampal neurogenesis in stressed rats at levels similar to imipramine treatment. Curcumin also reversed the stress-induced decrease in BDNF and 5-HT_{1A} mRNA levels across all hippocampal subfields. These effects were similar to those obtained from imipramine (Xu et al., 2007). Further evidence for the neuroprotective effects of curcumin was demonstrated in a recent study where pre-treatment with curcumin reversed the effect of corticosterone-induced neuronal changes in rats (Xu et al., 2011). Curcumin also attenuated quinolinate-induced excitotoxicity on primary cultures of human neurons (Braidy et al., 2011).

Depression and mitochondrial disturbances

Mitochondria are intracellular organelles found in most eukaryotic cells which generate most of the cell's supply of adenosine triphosphate (ATP). They are also involved in a range of other processes, such as signalling, cellular differentiation, cell death, as well as the control of the cell cycle and cell growth (McBride et al., 2006). Because of the brain's significant energy demands, high concentrations of mitochondria are found in this region making the brain susceptible to reductions in aerobic metabolism (Pieczenik and Neustadt, 2007).

Malfunction in the biochemical cascade and damage to the mitochondrial electron transport chain can lead to mitochondrial dysfunction or disease which has been implicated in a range of neuropsychiatric disorders such as depression, bipolar disorder and schizophrenia (Gardner and Boles, 2011; Rezin et al., 2009). In depression, mitochondrial disturbances such as deletions of mitochondrial DNA (Gardner and Boles, 2008a; Shao et al., 2008) and lower activities of respiratory chain enzymes and ATP production (Gardner et al., 2003) have been found. Gardner and Boles (2008a; 2008b) also showed that in depressed individuals with somatic complaints, the majority had lowered ATP production rates in biopsied muscles. Further support for mitochondrial dysfunction in depression is demonstrated by increased rates of depression in patients with mitochondrial disorders. For example, the lifetime diagnosis of depression in patients with mitochondrial disorders was 54% (Fattal et al., 2007). Greater rates of depression were also detected in adolescents with mitochondrial disorders (Koene et al., 2009).

It has been argued that because depression is associated with increased oxidative and nitrosative stress, increased inflammatory pathways, and lowered antioxidant defences, this may be a major cause of mitochondrial dysfunction in major depression (Gardner and Boles, 2011; Maes et al., 2012c). Kynurenine pathway metabolites such kynurenic acid, 3-

hydroxykynurenine and 3-hydroxyanthranilic acid, which are dysregulated in major depression, can also impair mitochondrial ATP production (Baran et al., 2003).

Effects of curcumin on mitochondrial function

Altering the pathogenic cascade associated with mitochondrial dysfunction in major depression may be a potential avenue to enhance treatment outcomes in depression. Curcumin, with its numerous molecular effects, may be a useful option with a number of studies demonstrating protective effects on mitochondria. Curcumin was able to attenuate oxidative damage in rat cortical neurons by reducing intracellular production of reactive oxygen species (ROS) and protecting mitochondria from oxidative damage (Zhu et al., 2004). Treatment with curcumin also lowered aluminium-induced oxidative stress and mitochondrial dysfunction in the rat brain, likely by several mechanisms such as activation of Heme oxygenase-1, maintenance of glutathione metabolism or by scavenging ROS (Sood et al., 2011). Curcumin and its analogues were also able to inhibit ROS-induced lipid peroxidation and protein damage in mitochondria (Wei et al., 2006). Nuclear factor erythroid 2-related factor 2 (Nrf2), which mediates neuroprotection against mitochondrial complex I and II inhibitors, is also activated by curcumin (Greco and Fiskum, 2010; Jiang et al., 2011)

Depression and nitric oxide

Nitric oxide (NO) is an intercellular messenger in the brain, synthesised from the amino acid L-arginine by the enzymatic action of nitric oxide synthase (NOS). Three NOS isoforms are known to exist in mammals — neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS) (Alderton et al., 2001). NO plays an important role in various physiological and pathological processes, and there has been increasing interest in its role in depression and other mental health conditions (Dhir and Kulkarni, 2011; McLeod et al., 2001;

Pinto et al., 2008). According to Dhir & Kulkarni (2011), support for a role of NO in the pathogenesis of major depression is provided by studies showing that levels of plasma NO and its metabolites are elevated in suicidal and depressed patients (Lee et al., 2006; Suzuki et al., 2001), evidence that decreasing or blocking the synthesis of NO can induce antidepressant-like effects (Joca and Guimaraes, 2006), research demonstrating that NO modulates the production of neurotransmitters such as noradrenaline, serotonin, and dopamine (Dhir and Kulkarni, 2011), and evidence of lower levels of nNOS in the locus coeruleus of people suffering from major depression than in normal controls (Karolewicz et al., 2004). Further indirect evidence for NO involvement in major depression is derived from the characterisation of circulating antibodies against NO-epitopes. Highly reactive substances such as NO-tyrosine, NO-tryptophan and NO-arginine are formed by nitration reactions, and increased IgM antibody levels against these NO-adducts have been found in depressed patients (Maes et al., 2008b; Maes et al., 2011d). These results suggest that increased NO and/or activation of nitration reactions and consequent increases in nitrated containing proteins may be involved in the pathophysiology of depression (Maes et al., 2011a).

Effects of curcumin on nitric oxide

Several studies have now confirmed that curcumin can regulate levels of nitric oxide. Immobilisation-induced restraint stress lasting six hours significantly increased plasma nitrite levels in mice, which was attenuated by intraperitoneal delivery of curcumin. This effect was enhanced when curcumin was jointly delivered with aminoguanidine, an iNOS inhibitor, thereby suggesting curcumin's possible inhibitory effect on iNOS (Gilhotra and Dhingra, 2010). In cultured human neurons, quinolinic acid induced nNOS activity and consequently increased nitrite levels. Curcumin dose-dependently decreased nNOS activity in human neurons (Braidy et al., 2010). Further evidence of curcumin's nitric oxide inhibitory effect was

demonstrated in a study on rats subjected to 72 hours of sleep deprivation. This led to increases in nitrite levels, along with several markers of oxidative damage. Intraperitoneal treatment with curcumin for 5 days had anxiolytic effects and restored nitrite levels. This effect was, however, abolished by pre-treatment with L-arginine, a precursor to nitric oxide, but only with the lower dose of curcumin of 10mg/kg. The researchers concluded that nitric oxide modulation is involved in the protective effect of curcumin in ameliorating sleep deprivation-induced behavioural alterations and oxidative damage (Kumar and Singh, 2008).

Depression and oxidative stress

In a review paper, Maes et al. (2011a) confirmed that major depression was accompanied by a decreased antioxidant status and by the induction of oxidative and nitrosative pathways. This was supported by studies showing significantly reduced plasma concentrations of important antioxidants such as vitamin C (Khanzode et al., 2003), vitamin E (Maes et al., 2000; Owen et al., 2005), and coenzyme Q_{10} (Maes et al., 2009b) in depressed patients. Depression was also accompanied by a lowered total antioxidant status (Cumurcu et al., 2009; Sarandol et al., 2007) and reduced antioxidant enzyme activity such as glutathione peroxidase (Maes et al., 2011e). Such deficiencies can impair protection against reactive oxygen species (ROS), causing damage to fatty acids, proteins and DNA (Maes et al., 2011a). In fact, increased levels of malondialdehyde, a measure of lipid peroxidation, were found in depressed patients (Ozcan et al., 2004; Sarandol et al., 2007; Wei et al., 2009), as have increased levels of 8-hydroxy-2-deoxyguanosine (8-OH-dG), a measure of oxidative damage to DNA (Forlenza and Miller, 2006; Maes et al., 2009a).

Further support for an association between oxidative stress and depression is provided by a few studies that demonstrate antioxidant properties of antidepressant medications. However, not all studies have uniformly identified reductions in oxidative markers following

antidepressant medications, necessitating further research in this area (Ng et al., 2008). Clinical studies into the efficacy of antioxidant therapies to alleviate depressive symptoms are lacking although N-acetylcysteine (NAC), a powerful antioxidant, was found to be useful for depressive episodes in bipolar disorder (Magalhaes et al., 2011). Zinc, which serves as a strong antioxidant, also has evidence of antidepressant activity (Szewczyk et al., 2011).

Antioxidant effects of curcumin

Investigations into the pharmacodynamics of curcumin have consistently demonstrated it to be a potent antioxidant (Ak and Gulcin, 2008; Menon and Sudheer, 2007), at least ten times more active as an antioxidant than vitamin E (Ak and Gulcin, 2008). In relation to a selection of the oxidative markers associated with depression, curcumin is able to lower levels of malondialdehyde (Rai et al., 2010), 8-OH-dG (Naik et al., 2011; Rai et al., 2010; Shih and Lin, 1993), and increase the activity of the antioxidant enzymes superoxide dismutase and glutathione peroxidase (Manikandan et al., 2011; Naik et al., 2011). Curcumin also attenuated increased markers of oxidative stress in rats undergoing chronic stress (Bhatia et al., 2011). In recent studies, curcumin also up-regulated Nrf2, a transcription factor that induces the expression of various genes including those that encode for several antioxidant enzymes (Scapagnini et al., 2011; Yang et al., 2009).

Depression and intestinal hyperpermeability

The intestinal epithelium is the largest mucosal surface in the human body and provides an interface between the external environment and the host (Fasano and Shea-Donohue, 2005). Normally, the intestinal epithelium provides a semi-permeable wall which allows nutrients to be absorbed while preventing larger, potentially toxic, antigenic, or pathogenic molecules or organisms from passing into the bloodstream. However, the permeability of the intestinal

epithelium can become compromised leading to a condition known as intestinal hyperpermeability or 'leaky gut.' This results in an increased diffusion of antigenic food molecules and translocation of bacteria from the gut into extra-intestinal sites which can then trigger an immune response (Miller, 1997).

Lipopolysaccharides (LPS) are large molecules found in the outer membrane of Gram-negative bacteria and, during a state of intestinal hyperpermeability, are known to translocate into the systemic circulation in greater quantities (Maes et al., 2008a). Once the LPS are translocated into the blood, an inflammatory process is generated and is associated with increased neuroinflammation and secretion of proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α (Dunn, 2006; Henry et al., 2008; Huang et al., 2008; Qin et al., 2007). LPS are also able to activate IDO production leading to increased kynurenine metabolites and tryptophan breakdown (Dobos et al., 2012; Fu et al., 2010; O'Connor et al., 2009).

Research into the relationship between LPS, intestinal permeability and depression has demonstrated that LPS have the capacity to induce depressive behaviour in animals (Henry et al., 2008; Yirmiya, 1996). Interestingly, antidepressants such as fluoxetine and imipramine attenuate behavioural responses to immune challenges, such as LPS (Yirmiya et al., 2001). In a recent study, the reverse was demonstrated where LPS reduced the antidepressant effects of fluoxetine in a chronic, unpredictable mild stress model in mice (Wang et al., 2011).

Investigations into the incidence of intestinal hyperpermeability in patients with major depressive disorder have confirmed an increased translocation of LPS from Gram- negative enterobacteria in depressed patients. This was demonstrated by increased serum IgM and IgA levels directed against LPS of Gram-negative enterobacteria (Maes et al., 2012b; Maes et al., 2008b). Maes and colleagues concluded that depressive disorder was accompanied by

increased gut permeability which was associated with an immune response directed against LPS produced by enterobacteria.

Effects of curcumin on the LPS-induced immune response

Several studies have investigated the protective effects of curcumin on LPS administration. In two separate studies, curcumin decreased NO production in LPS-stimulated microglial cells in a dose-dependent manner (Jung et al., 2006; Tocharus et al., 2012). Both pre- and post-treatment with curcumin diminished LPS-induced dopamine neurotoxicity in a dose-dependent manner. LPS-induced production of many proinflammatory factors and their gene expressions such as TNF-α, NO, PGE_2 and IL-1β was also dramatically reduced following curcumin treatment. Curcumin also decreased LPS-induced activation of two transcription factors - nuclear factor kappaB and activator protein-1 (Huang et al., 2008). The benefits of curcumin may also occur through its ability to reduce the translocation of bacteria into extraintestinal sites, such as mesenteric lymph nodes, liver, spleen, and/or bloodstream (Karatepe et al., 2010)Given the potential of LPS to induce depressive-like behaviour in animals, and an increased translocation of LPS in depressed patients resulting from increased intestinal hyperpermeability, the ameliorating effects on LPS-induced inflammation provides another potential antidepressant mode of action of curcumin.

Conclusion

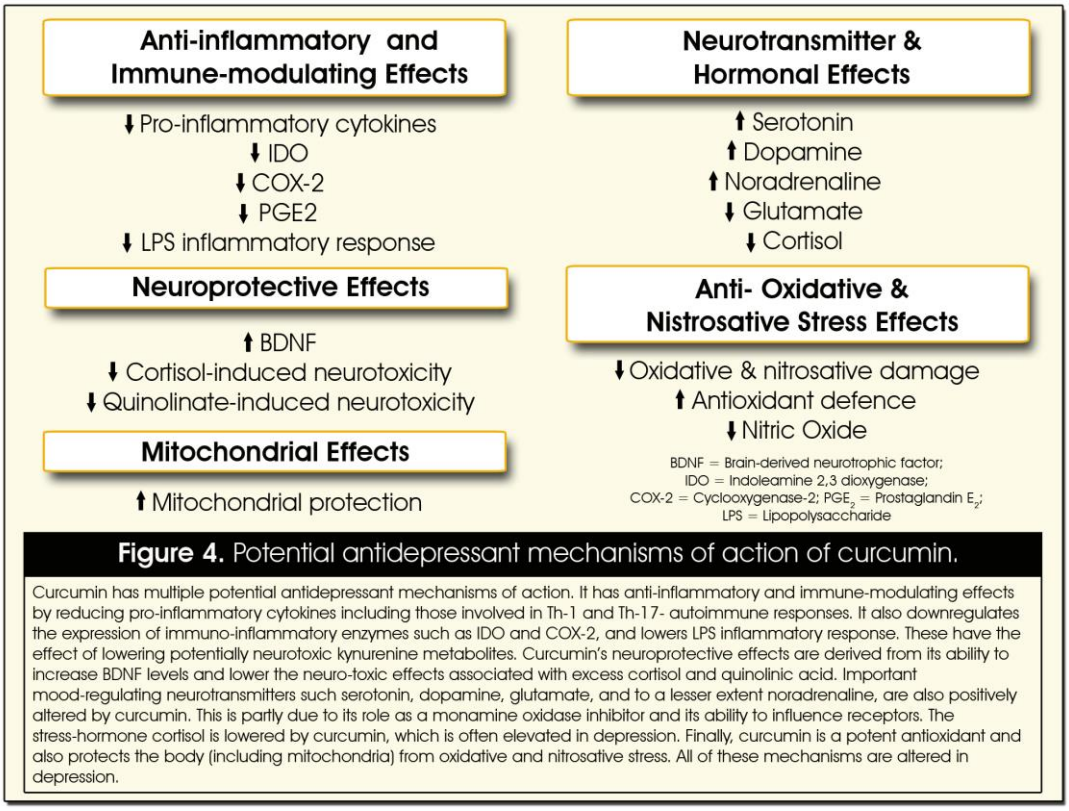

Figure 4. Potential antidepressant mechanisms of action of curcumin.

Curcumin has multiple potential antidepressant mechanisms of action. It has anti-inflammatory and immune-modulating effects by reducing pro-inflammatory cytokines including those involved in Th-1 and Th-17- autoimmune responses. It also downregulates the expression of immuno-inflammatory enzymes such as IDO and COX-2, and lowers LPS inflammatory response. These have the effect of lowering potentially neurotoxic kynurenine metabolites. Curcumin's neuroprotective effects are derived from its ability to increase BDNF levels and lower the neuro-toxic effects associated with excess cortisol and quinolinic acid. Important mood-regulating neurotransmitters such serotonin, dopamine, glutamate, and to a lesser extent noradrenaline, are also positively altered by curcumin. This is partly due to its role as a monamine oxidase inhibitor and its ability to influence receptors. The stress-hormone cortisol is lowered by curcumin, which is often elevated in depression. Finally, curcumin is a potent antioxidant and also protects the body (including mitochondria) from oxidative and nitrosative stress. All of these mechanisms are altered in depression.

While clinical trials on the antidepressant effects of curcumin are required to determine the efficacy of this natural substance, this paper highlights the multiple potential antidepressant modes of action of curcumin. As discussed above and summarised in Figure 4, curcumin has been shown through *in vitro* and *in vivo* studies to influence a range of neurotransmitters and hormones commonly observed to be disturbed in major depression. It also has the potential to provide neuroprotective effects, and shows some promise as a protective agent from stress-induced neurotoxicity. Curcumin's anti-inflammatory and antioxidant effects are already well-recognised and may prove to be another potential mode of action in treating depression.

Unfortunately, a commonly cited problem associated with curcumin relates to its poor bioavailability via oral ingestion, limiting its potential clinical application (Anand et al., 2007). However, recent efforts to enhance its bioavailability have shown significant promise. For example, blood levels of the patented formulation BCM-95®CG was found to be 6.93 times

higher than standard curcumin, and 6.3-fold higher than a curcumin-lecithin-piperine formula (Antony et al., 2008). In another human study on the patented curcumin formula, Meriva®, its total curcuminoid absorption was shown to be 29-fold higher than an unformulated curcuminoid mixture (Cuomo et al., 2011). Curcumin administered with the agent piperine also increases oral bioavailability (Shoba et al., 1998). While no research has yet assessed whether this increased absorption is associated with increased clinical efficacy, it is hoped that these methods of delivery may at least partly overcome problems associated with curcumin's poor oral absorption and therefore enhance its utility in clinical settings.

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Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study

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Abstract

BACKGROUND: Curcumin, the principal curcuminoid derived from the spice turmeric, influences several biological mechanisms associated with major depression, namely those associated with monoaminergic activity, immune-inflammatory and oxidative & nitrosative stress pathways, hypothalamus-pituitary-adrenal (HPA) axis activity and neuroprogression. We hypothesised that curcumin would be effective for the treatment of depressive symptoms in individuals with major depressive disorder.

METHODS: In a randomised, double-blind, placebo-controlled study, 56 individuals with major depressive disorder were treated with curcumin (500 mg twice daily) or placebo for 8 weeks. The primary measure was the Inventory of Depressive Symptomatology self-rated version (IDS-SR30). Secondary outcomes included IDS-SR30 factor scores and the Spielberger State-Trait Anxiety Inventory (STAI).

RESULTS: From baseline to week 4, both curcumin and placebo were associated with improvements in IDS-SR30 total score and most secondary outcome measures. From weeks 4 to 8, curcumin was significantly more effective than placebo in improving several mood-related symptoms, demonstrated by a significant group x time interaction for IDS-SR30 total score ($F_{1,53} = 4.22$, $p = .045$) and IDS-SR30 mood score ($F_{1,53} = 6.51$, $p = .014$), and a non-significant trend for STAI trait score ($F_{1,48} = 2.86$, $p = .097$). Greater efficacy from curcumin treatment was identified in a subgroup of individuals with atypical depression.

CONCLUSIONS: Partial support is provided for the antidepressant effects of curcumin in people with major depressive disorder, evidenced by benefits occurring 4 to 8 weeks after treatment.

LIMITATIONS: Investigations with larger sample sizes, over extended treatment periods, and with varying curcumin dosages are required.

Introduction

Disturbances in monoaminergic neurotransmission, particularly around serotonin availability, were originally posited as the primary cause of major depression (Cowen, 2008). However, studies now confirm that major depression is associated with a large array of biological disturbances. These include dysregulation in the hypothalamus-pituitary-adrenal (HPA) axis, activation of immune-inflammatory pathways, increased oxidative and nitrosative stress, neuroprogression, and mitochondrial dysfunction (Leonard and Maes, 2012; Maes et al., 2011c). Consequently, this has sparked interest in compounds that target these pathways. Examples include anti-inflammatory treatments influencing immuno-inflammation such as cyclooxygensase-2 (COX-2) inhibitors, aspirin, minocycline and polyunsaturated fatty acids (Berk et al., 2013a; Fond et al., 2014; Muller, 2013) and antioxidant therapies to increase antioxidant defences and lower free radical damage such as n-acetyl cysteine, Ebselen, vitamin E and coenzyme-Q_{10} (Berk et al., 2013b; Scapagnini et al., 2012). Interestingly, despite pharmaceutical antidepressants originally being heralded as targeting monoaminergic actions, there is also evidence that they can modulate immuno-inflammation, reduce oxidative stress, enhance neurotrophic factors and influence HPA activity (Abdel-Wahab and Salama, 2011; Andrade and Rao, 2010; Hannestad et al., 2011a; Kocki et al., 2012; Schule, 2007).

Curcumin is the most active compound of the Indian spice turmeric and comprises 2-8% of most turmeric preparations (Sharma et al., 2005). Curcumin [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a low molecular weight polyphenol, first chemically characterised in 1910 by Milobedzka *et al*. (1910) and influences all of the aforementioned biological mechanisms (Aggarwal and Harikumar, 2009; Lopresti et al., 2012). More specifically, curcumin is a potent antioxidant that can lower markers of oxidative stress (Naik et al., 2011; Rai et al., 2010), modulate immuno-inflammation by acting as a COX-2

inhibitor (Lee et al., 2011; Plummer et al., 1999) and lower pro-inflammatory cytokines (Basnet and Skalko-Basnet, 2011; Belcaro et al., 2010), provide significant neuroprotection (Huang et al., 2011; Xu et al., 2007), modulate HPA activity (Huang et al., 2011; Li et al., 2009) and influence monoamine transmission through its effect on serotonergic and dopaminergic activity (Bhutani et al., 2009; Kulkarni et al., 2008; Xia et al., 2007). In animal studies, antidepressant effects of curcumin have been attributed to its serotonergic, dopaminergic, neuroprotective and HPA-modulating effects (Huang et al., 2011; Kulkarni et al., 2008; Xu et al., 2006). Two clinical trials have also now been completed investigating the antidepressant effects of curcumin in people with major depression. In the first study, curcumin as an add-on to antidepressant therapy did not enhance treatment outcome (Bergman et al., 2013), whereas in the second trial curcumin demonstrated similar antidepressant efficacy to fluoxetine (Sanmukhani et al., 2014). However, the latter study lacked a placebo-control and volunteers were not blinded.

The purpose of this study was to expand investigation into the antidepressant effects of curcumin supplementation in people with major depressive disorder. It was hypothesised that treatment with curcumin would lead to greater antidepressant benefits than a placebo, reflected by reductions in the administered depression and other mood-related self-report questionnaires. Curcumin was also hypothesised to have greater benefits for participants with atypical depression as it is associated with dysregulated immune-inflammatory pathways (Hickman et al., 2013; Lamers et al., 2013).

Materials and Methods

Study design

This study was an 8-week, randomised, double-blind, placebo-controlled clinical trial (Figure 1). The trial protocol was approved by the Human Research Ethics Committee at

Murdoch University, Western Australia. The trial was registered with the Australian New Zealand Clinical Trials Registry (no. 12612001260819) and participants were recruited between February and November 2013, across the Perth, Western Australia metropolitan area. Recruitment occurred through advertisements and promotions in community newspapers and a health magazine, and after interviews with local radio media outlets.

Participants were randomly and equally allocated into two groups (placebo and curcumin) using a randomisation calculator (http://www.randomization.com). Both curcumin and placebo capsules were packed in identical containers labelled by participant code numbers and were allocated according to order of participant enrolment in the study.

Participants

Inclusion criteria: Male and female participants aged 18 to 65 years were eligible to participate if they met the DSM-IV criteria for current major depressive disorder and had an Inventory of Depressive Symptomatology self-rated version ($IDS\text{-}SR_{30}$) score ≥ 14. The diagnosis of major depression was made by the first author, an experienced clinical psychologist, using The Mini International Neuropsychiatric Interview 6.0 (MINI 6.0) (Sheehan et al., 1998). Pharmaceutical antidepressants, the use of the contraceptive pill and no more than once a week use of analgesics were permissible. If participants were on pharmaceutical antidepressants, the drug dosage or type must have been stable for the past 8 weeks and throughout the duration of the study. Only non-smokers were included in the study and volunteers were not currently taking turmeric/ curcumin supplements. If volunteers were receiving psychological therapy, the treatment must have commenced at least 8 weeks prior to participating in the study.

Exclusion criteria: participants with a psychotic disorder, bipolar disorder, comorbid obsessive-compulsive disorder, posttraumatic stress disorder, eating disorder, or any

substance abuse or dependence disorder were excluded, as were participants assessed as having high risk of suicide. Volunteers were also excluded if they suffered from medical illnesses including diabetes, autoimmune diseases, cardiovascular disease, hypertension, neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease, stroke, and multiple sclerosis), chronic fatigue syndrome, fibromyalgia and asthma; were pregnant or intended to fall pregnant; currently breastfeeding; had suffered from an infection or illness over the past month; were currently taking any antiplatelet or anticoagulant medications; or had been diagnosed with any coagulation disorder.

Interventions

Placebo (cellulose) and curcumin capsules were supplied by Arjuna Natural Extracts Ltd. (Kochi, India), and were identical in appearance. Curcumin was provided in a 500 mg capsule (BCM-95®) containing total curcuminoids 88% (curcumin, bisdemethoxycurcumin, demethoxycurcumin) and volatile oils 7% from rhizomes of *Curcuma longa* Linn. Participants were directed to take one capsule, twice daily with or without food for 8 weeks. Curcumin was used at a dose of 1000 mg/day. Medication compliance was measured by volunteer-reported pill count at weeks 4 and 8.

Outcomes

Self-report questionnaires

Inventory of Depressive Symptomatology self-rated version (IDS-SR$_{30}$): The IDS-SR$_{30}$ was used as the primary outcome measure. It contains 30 items measuring depressive symptoms based on the DSM-IV criteria for major depressive episode (Rush et al., 1986; Rush et al., 1996). Respondents are asked to rate the severity and frequency of specific symptoms present over the past 7 days. The IDS-SR$_{30}$ has acceptable psychometric properties in depressed outpatients (Rush et al., 2000; Rush et al., 1996; Trivedi et al., 2004) and correlates highly with common

depression inventories such as the $HRSD_{17}$, BDI, and MADRS (Corruble et al., 1999; Rush et al., 2000; Rush et al., 1996).

In a factor analytical study on the $IDS\text{-}SR_{30}$, two dimensions were identified: a 'mood/cognition' factor representing affective and cognitive symptoms (IDSm), and an 'anxiety/arousal' factor indicating arousal and somatic complaints (IDSa) (Wardenaar et al., 2010). In addition, items in the $IDS\text{-}SR_{30}$ associated with 'atypical' and 'melancholic' depression have been used for the clinical subtyping of these two subtypes of depression (Gili et al., 2012). This item analysis was used to categorise volunteers into atypical or melancholic depression.

The Spielberger State-Trait Anxiety Inventory (STAI): The STAI is a self-report tool for assessing anxiety consisting of two subscales (state and trait anxiety) each containing 20 items (Spielberger, 1983). The STAI is among the most widely researched and commonly used measures of general anxiety and has good reliability and validity (Metzger, 1976; Okun et al., 1996). The STAI was considered an appropriate measure given its strong correlation with measures of depression (Kennedy et al., 2001).

Statistical analysis

Treatment condition on mood measures

Two successive analyses were conducted. The first compared curcumin versus placebo groups. Second, as an exploratory analysis, volunteers with atypical depression were compared across treatment groups (curcumin versus placebo). Analysis of volunteers with melancholic depression could not be completed due to limited numbers (n = 3).

Independent samples t-tests were used to compare demographic variables across the treatment groups for continuous variables, and Pearson Chi-squared tests (or Fisher exact test for low cell counts) were used to compare categorical data. Individual mood measures (IDS-

SR_{30}, STAI, and relevant sub-scores) were assessed for differences between baseline, mid-point (week 4) and end-point (week 8) by a mixed repeated-measures analysis of variance (ANOVA).

Analyses for time (baseline, midpoint and post-treatment) within each treatment condition, and treatment (curcumin and placebo) x time (baseline, midpoint and post-treatment) effects were conducted. Planned contrasts were also conducted to compare mood changes at differing time points (i.e., baseline to week 4; week 4 to week 8). There were no significant outliers in data as assessed by the visual inspection of Q-Q plots, although questionnaire data was not normalised. The repeated measures ANOVA was considered appropriate for statistical analyses as it is relatively robust to violations of normality when group sample sizes are equivalent (Tabachnick and Fidell, 2007). Data from all participants were included in analyses (intention to treat, with multiple imputation for missing values).

For all the tests, statistical significance was set at $P< 0.05$ (two-tailed). All data were analysed using SPSS (version 21; IBM, Armonk, NY).

Results

Study Population

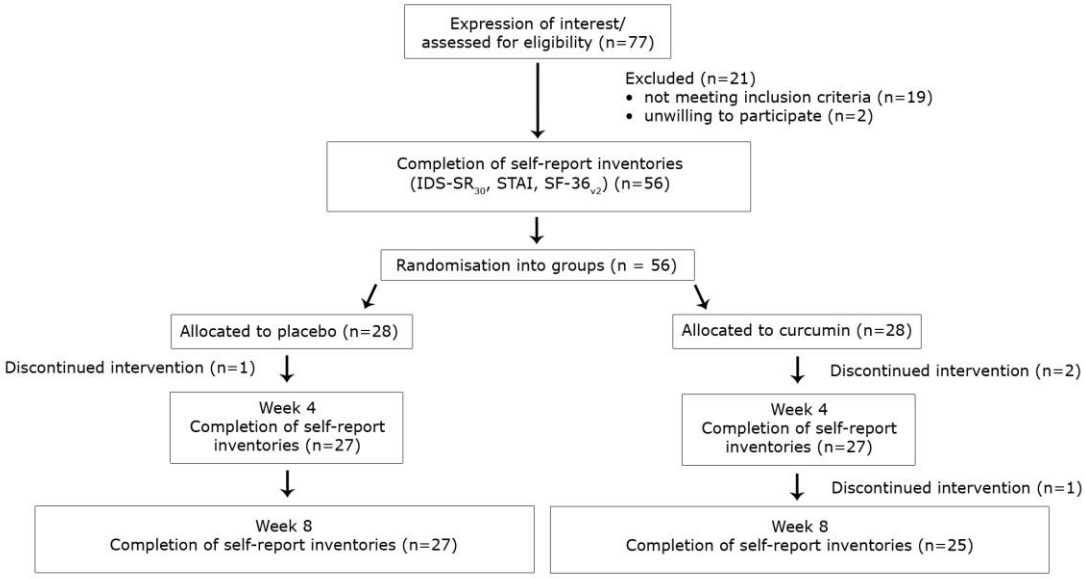

Figure 1: Systematic illustration of study design

Baseline questionnaire and demographic information

Seventy-seven people were screened for participation in the study and 56 met inclusion/ exclusion criteria and were enrolled to participate. Twenty-eight people were randomised into the placebo group and 28 into the treatment (curcumin) group. Fifty-two participants completed up to week 8. There were 4 drop-outs, one from the placebo group and three from the curcumin group, with no significant difference between the dropout rate in each group. Reasons for withdrawal included an unexpected visit overseas for family purposes (1 in the curcumin group), flare up of digestive complaints (1 in the curcumin group), and inconsistent intake of allocated capsules (1 each in the curcumin and placebo group). As shown in Tables 1 and 2, there were no significant differences between the two groups for any baseline mood questionnaire scores or demographic variables, except for distribution of medical illnesses, with greater reported medical illnesses in the placebo (n=15) versus curcumin (n=5) group (X^2

(1) = 7.78, *p*- = .011). Medical illness was therefore included as a covariate in the repeated measures ANOVA analyses.

Table 1. Demographic characteristics of curcumin and placebo participants.

	Placebo n=28	Curcumin n=28	p-value
Age, years mean (SD)	48.54 (11.73)	44.04 (11.94)	0.16[†]
BMI (kg/m²)mean (SD)	27.06 (4.76)	26.12 (5.48)	0.51[†]
Sex *n*			
Female	20	20	1.00[#]
Male	8	8	
Marital Status *n*			
Single	7	11	
Married	12	11	
De facto[*]	5	4	.551[#]
Divorced	2	2	
Widowed	2	0	
Educational Status *n*			
Secondary	6	9	
Tertiary	17	15	.658[#]
Post-graduate	5	4	
General Health *n*			
Great	9	7	
Average	19	18	.194[#]
Poor	0	3	
Medical Illness *n*			
Yes	15	5	.011[#]
No	13	23	
Antidepressant Medication *n*			
Yes	9	10	1.00[#]
No	19	18	
Antidepressant class *n*			
SSRI	7	6	.628[#]
SNRI	2	4	
Depression episodes *n*			
Single episode	11	7	.391[#]
Recurrent episodes	17	21	
Exercise Frequency *n*			
Never/Rarely	6	4	
1-2 times week	9	10	.421[#]
3-5 times week	11	14	
6+ times week	2	0	
Injuries causing regular pain *n*			
Yes	14	10	.418[#]
No	14	18	

[*]Domestic partner outside marriage

[†]Independent samples T-test; [#]Chi-square Test

SSRI= selective serotonin reuptake inhibitor; SNRI= selective serotonin-norepinephrine reuptake inhibitor

Table 2. Baseline questionnaire scores between curcumin and placebo participants.

	Placebo n=28 mean (SD)	Curcumin n=28 mean (SD)	p-value†
STAI state	50.25 (13.02)	52.00 (13.17)	0.62
STAI trait	55.89 (13.24)	56.29 (8.30)	0.90
IDS	33.14 (9.39)	33.04 (9.39)	0.97
IDS mood	14.64 (5.67)	13.93 (5.37)	0.63
IDS arousal	6.68 (2.79)	6.82 (2.40)	0.84

†Independent samples T-test
Data are shown as mean (SD)

Exploratory analyses were conducted on 18 participants identified as suffering from atypical depression (placebo, n =8; curcumin, n=10). There were no significant differences between the two treatment groups for any baseline mood questionnaires. Demographic characteristics were also similar across treatment groups, except for differences in mean age (placebo, x = 50.75; curcumin, x = 40.80). The difference, 9.95, 95% CI [0.81, 19.09] was significant ($t(16) = 2.31$, $p = .035$). Age was therefore included as a covariate in repeated measures ANOVA analyses on the atypical depression sample.

Outcome Measures

Treatment effects on mood measures

IDS – Depression measures

Changes in IDS scores across both treatment groups and repeated measures ANOVA significance values are listed in Table 3. There was a significant reduction in all IDS scores across both groups for time although there were no significant group x time interactions for any IDS measure across the full 8 weeks of treatment. However, contrasts revealed a significant group x time interaction from week 4 to week 8 for IDSm ($F_{1,53} = 6.51$, $p = .014$) and IDS total ($F_{1,53} = 4.22$, $p = .045$).

Further ANOVA analyses revealed that from baseline to week 4 there were significant changes in all IDS scores, in both the curcumin and placebo group. However, there were no significant changes in any IDS scores from week 4 to week 8 in the placebo group. In the curcumin group, there were significant changes in IDS total ($F_{1,27} = 5.50$, $p = .026$), and IDSm ($F_{1,27} = 6.07$, $p = .020$) over this time. This indicates that in the placebo group, all improvements in IDS depressive scores occurred in the first 4 weeks of treatment, while improvements continued in the curcumin condition.

Table 3. Changes in questionnaire scores over time.

								Treatment x Time effect (p-value)		
	Treatment	Baseline		Week 4		Week 8		Baseline-week 4	week 4- week 8	Baseline - week 8
STAI- State, mean (SD)	Placebo (n=28)	50.25	(13.02)	43.14[b]	(13.30)	43.21[f]	(12.94)	.687	.255	.595
	Curcumin (n=28)	52.00	(13.17)	45.89[b]	(12.65)	42.29[d,g]	(12.21)			
STAI- Trait, mean (SD)	Placebo (n=28)	55.89	(13.25)	49.82[b]	(12.79)	50.21[f]	(9.41)	.516	.097	.358
	Curcumin (n=28)	56.29	(8.30)	50.75[c]	(9.46)	47.96[d,f]	(11.32)			
IDS - Total, mean (SD)	Placebo (n=28)	33.14	(11.88)	25.82[c]	(14.55)	25.89[f]	(13.43)	.313	.045*	.189
	Curcumin (n=28)	33.04	(9.39)	26.61[c]	(11.87)	22.71[d,f]	(9.36)			
IDS- Mood, mean (SD)	Placebo (n=28)	14.64	(5.67)	10.50[c]	(6.88)	11.00[f]	(6.60)	.496	.014*	.192
	Curcumin (n=28)	13.93	(5.37)	11.00[c]	(5.34)	9.25[d,f]	(4.42)			
IDS- Arousal, mean (SD)	Placebo (n=28)	6.68	(2.79)	5.64[c]	(3.37)	5.25[e]	(3.12)	.282	.312	.489
	Curcumin (n=28)	6.82	(2.40)	5.57[c]	(3.18)	4.71[f]	(2.81)			

Medical illness included as covariate

[a]$p < .05$; [b]$p < .01$; [c]$p < .001$ - within group significant time effects from baseline to week 4

[d]$p < .05$ - within group significant time effects from week 4 to week 8

[e]$p < .01$; [f]$p < .001$ - within group significant time effects from baseline to week 8

STAI – Anxiety measures

Changes in STAI scores across both treatment groups and repeated measures ANOVA significance values are listed in Table 3. There were significant reductions in STAIs and STAIt scores across both groups for time (p<0.001; for all scores across time). There were no significant group x time interactions for either STAIs or STAIt across the full 8 weeks of treatment.

Further ANOVA analyses revealed that from baseline to week 4 there were significant changes in both STAIs and STAIt scores, in both the curcumin and placebo group. However, from week 4 to week 8, in the placebo group, there were no significant changes in either score. In the curcumin group, there was a significant change in STAIt ($F_{1,27}$ = 4.36, p = .046), and non-significant trend for STAIs ($F_{1,27}$ = 3.64, p = .067) over this time. This indicates that in the placebo group, improvements in STAI anxiety scores occurred in the first 4 weeks of treatment, while improvements continued in the curcumin condition.

Atypical Depression Sub-group

IDS – Depression measures

There was a significant reduction in most IDS scores across both groups for time. In the placebo group, there were significant time effects for IDS total (p<0.05), IDSm (p<0.05), but not IDSa (p>0.05). In the curcumin group, there were significant time effects for IDS total (p<0.01), IDSm (p<0.001), and IDSa (p<0.01). There were no significant group x time interactions in any IDS measure across the full 8 weeks of treatment (IDSm, $F_{2,32}$ = 2.40, p = .110; IDSa $F_{2,32}$ = 0.62, p = .670) although there was a non-significant trend for IDS total ($F_{2,32}$ = 2.73, p = .088). Contrasts revealed a significant group x time interaction from week 4 to week 8 for IDS total ($F_{1,16}$ = 7.78, p = .013) and IDSm ($F_{1,16}$ = 10.61, p = .006).

In Figure 2, changes in IDS scores are detailed for each treatment condition. Further ANOVA analyses revealed that from baseline to week 4 there were significant changes in IDS total ($F_{1,7} = 6.13$, $p = .043$) in the placebo group. In the curcumin group there were significant changes in IDS total ($F_{1,9} = 8.74$, $p = .016$), IDSm ($F_{1,9} = 10.30$, $p = .011$) and IDSa ($F_{1,9} = 9.11$, $p = .015$) over this time period. From week 4 to week 8, there were no further significant changes in any IDS score in the placebo group. However, in the curcumin group there were significant changes in IDS total ($F_{1,9} = 8.62$, $p = .017$), IDSm ($F_{1,9} = 9.86$, $p = .012$), and IDSa ($F_{1,9} = 6.42$, $p = .032$) scores over this time. This indicates that in the placebo group, all improvements in IDS depressive scores occurred in the first 4 weeks of treatment, while improvements continued in the curcumin condition.

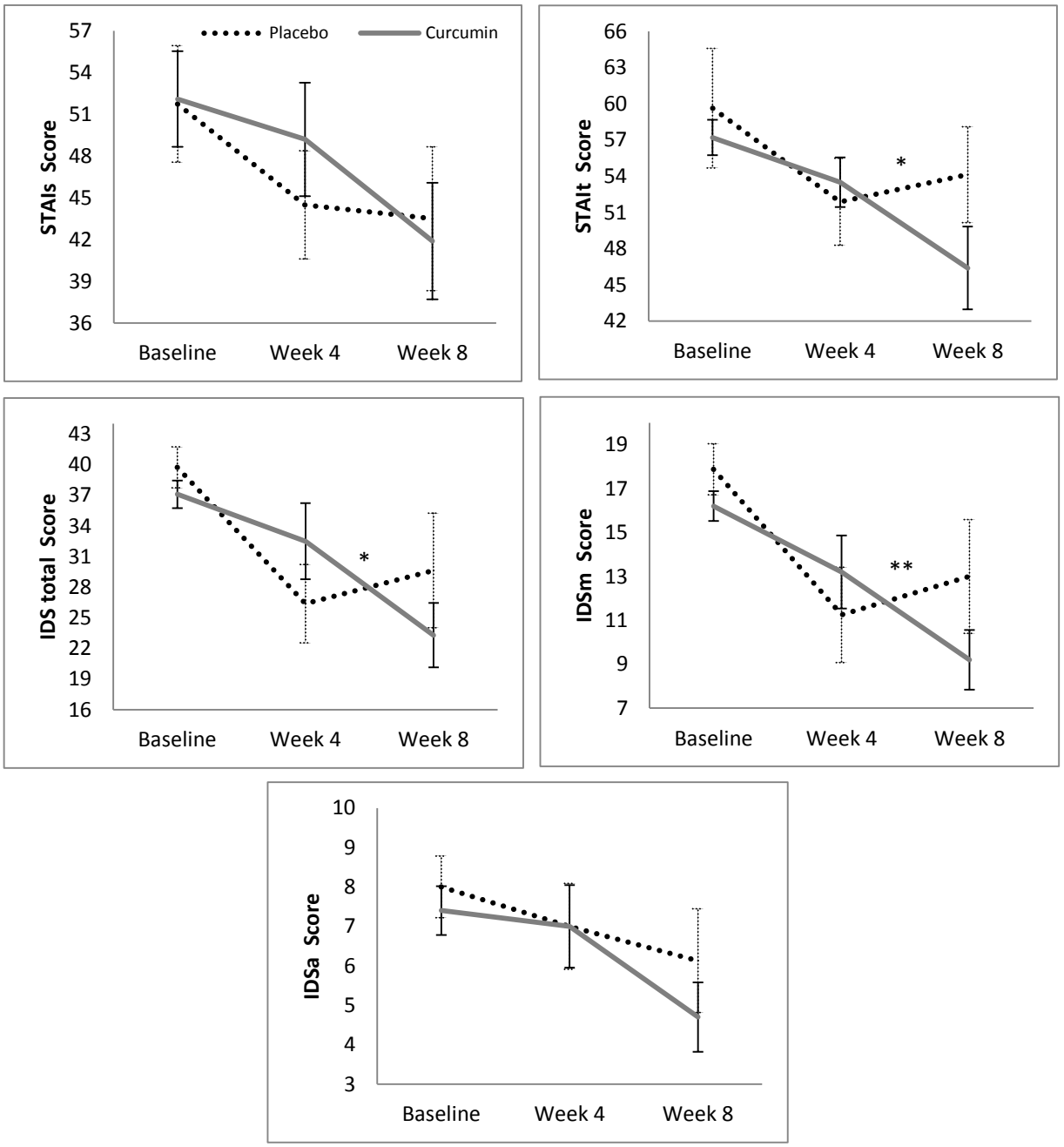

Figure 2. Atypical depression - Change in mood scores over time (± 1 *Std. error)* across curcumin and placebo groups. * (p<.05); **(p<.01) indicates significant group x time interaction for specified period

STAI – Anxiety measures

There were significant reductions in STAIs and STAIt scores across both groups for time (p<0.001; for all scores across time). There was no significant group x time interactions for

either STAIs across the full 8 weeks of treatment. However, contrasts revealed a significant group x time interaction from week 4 to week 8 for STAIt ($F_{1,15} = 6.00$, $p = .027$). In Figure 2, changes in STAI scores are detailed for each treatment condition. Further ANOVA analyses revealed that from baseline to week 4 there were significant changes in STAIt scores, in the curcumin group only ($F_{1,9} = 11.62$, $p = .008$). Continued significant changes in STAIt occurred from weeks 4 to 8 in the curcumin group only ($F_{1,9} = 7.24$, $p = .025$).

Adverse events

Details of adverse events reported by participants are included in Table 4. All reported adverse events were of minor severity and only one participant in the curcumin intervention withdrew from the study as a result of reported side effects. This participant experienced an exacerbation of pre-existing digestive complaints (stomach bloating and pain). There were no significant differences between reported adverse events between placebo and curcumin groups.

Table 4: List and frequency of adverse events reported by participants.

CURCUMIN		PLACEBO	
Frequency	Reported complaints	Frequency	Reported complaints
16	No adverse events	14	No adverse events
7	Digestive: stomach bloating, nausea, mild diarrhoea	6	Digestive: appetite change, bloating, mild diarrhoea
0	Respiratory: none	1	Respiratory: breathing problems
3	Dermatological: dry skin, flaking skin	2	Dermatological: dry skin, flaking skin, itchy skin
2	Neurological: headaches, dizziness	2	Neurological: memory slower, tingling in hands
2	Pain: joint pain, back pain	4	Pain: joint pain, back pain, neck pain
2	Cardiovascular: racing heart, chest pain	0	Cardiovascular: none
3	Visual: sore eyes, dry eyes, blurry vision	0	Visual: none
1	Auditory: ringing in ears	2	Auditory: ringing in ears
2	Oral: dry mouth, sore gums	2	Oral: dry mouth, mouth ulcers

Discussion

The results of this study provide partial support for the antidepressant and anxiolytic effects of curcumin in people suffering from major depressive disorder. While curcumin and placebo were equally effective in reducing depressive and anxiety symptoms in the first four weeks of treatment, curcumin was significantly more effective than placebo in lowering self-reported depressive and anxiety symptoms from weeks 4 to 8. When examining the effects of curcumin in people with atypical depression, curcumin had even greater antidepressant and anti-anxiety efficacy compared to placebo. Again, equivalent improvements in mood occurred from baseline to week 4 in both placebo and curcumin-treated individuals. However, from weeks 4 to 8, curcumin was significantly more effective in lowering total depressive symptoms (total IDS score), mood/cognitive depressive symptoms (IDSm), arousal-related symptoms (IDSa) and trait anxiety (STAIt).

While greater antidepressant effects of curcumin compared to placebo were observed from weeks 4 to 8, when evaluating the whole treatment period (i.e., baseline to week 8), curcumin was not found to be significantly more effective than placebo in reducing depressive and anxiety symptoms. Several explanations could account for this overall non-significant treatment effect: (1) it may be that curcumin lacks a true antidepressant effect in people with major depressive disorders, at least at the dose prescribed (i.e., 500mg twice daily). However, this argument is countered by significant and near significant changes in several mood measures in the second half of treatment; (2) it is a reflection of the placebo response, typical in placebo-controlled trials. From a statistical point of view, when performing the analyses on the whole treatment period, the positive placebo response in the first month of treatment masked the positive gains from curcumin over the second study period (weeks 4 to 8). Placebo responses in depression trials are common and it has been suggested that true drug

responses are characterised by a 2-week delay, with continued improvement thereafter, whereas placebo effects are characterised by abrupt, transient improvements (Rothschild and Quitkin, 1992). Although assessments were not completed until week 4, this study confirms a similar pattern of change – that is, in placebo-treated individuals, a response in the first month, followed by no change, or even worsening of symptoms thereafter. In contrast, curcumin-treated individuals continued to experience improvements over the course of the study; (3) the antidepressant effects of curcumin may not begin until after 4 weeks of intake, reflecting a slow acting, possibly longer term treatment for depression. It is feasible that specific mechanistic changes need to be set in motion and maintained for a period of time before mood changes prevail. The high portion of recurrent depressed sufferers enrolled in the study (approx. 70 percent) may also contribute to curcumin's slow action in this trial. These possibilities require exploration through follow-up studies with larger sample sizes, and extended treatment periods.

The antidepressant effects of curcumin in people with major depressive disorder have now been investigated in two additional randomised clinical trials. As an add-on to newly commenced antidepressant medication (escitalopram or venlafaxine XR), curcumin, at a dose of 500 mg/day, did not enhance treatment efficacy compared to a placebo (Bergman et al., 2013). In this double-blind, placebo controlled, 5-week trial, there were significant improvements in depressive symptoms over time in both treatment groups. In the second study, Sanmukhani *et al.* (2014) compared the antidepressant effects of curcumin alone (500 mg twice daily), fluoxetine alone (20 mg/day) or curcumin plus fluoxetine (500 mg twice daily and 20 mg/day, respectively) in people suffering from major depressive disorder. In this randomised, single-blinded (researcher masked), 6-week trial, all three treatment conditions were associated with significant improvements in depressive symptoms. Group comparisons revealed comparable treatment efficacy across the three conditions. Weaknesses associated

with this study include the lack of placebo control, and non-masking of participants from the treatment conditions.

The current study therefore adds to the aforementioned ones as the length of treatment was extended to 8 weeks, double-blind placebo controlled conditions were included, and curcumin was used a standalone treatment or was used in patients undergoing pre-existing, stabilised antidepressant or psychological therapies. Exploratory analyses on people with atypical depression were also conducted, and several questionnaires were used to assess depressive, anxiety and general health changes. Further support for the antidepressant effects of curcumin is provided by consistent findings of protective behavioural effects in animal models of depression and chronic mild stress (Jiang et al., 2013; Sanmukhani et al., 2011; Zhang et al., 2014).

An important finding from this study is the enhanced antidepressant and anxiolytic efficacy of curcumin in people with atypical depression. According to DSM-IV criteria, atypical depression is characterised by mood reactivity to actual or potential positive events, and two or more of the following features; significant weight gain or increased appetite, hypersomnia, leaden paralysis, and a long-standing pattern of interpersonal rejection sensitivity (American Psychiatric Association, 2000). Compared to healthy individuals, and people with melancholic or non-atypical depression, atypical depression is often associated with higher levels of inflammatory markers such as C-reactive protein (CRP) (Hickman et al., 2013; Lamers et al., 2013), IL-6 and tumour necrosis factor-α (TNF-α) (Lamers et al., 2013). Due to the anti-inflammatory effects of curcumin, it is this immuno-inflammatory dysregulation that may account for the increased efficacy of curcumin in people with atypical depression. In a recent meta-analysis on clinical trials it was concluded that curcumin lowers CRP levels (Sahebkar, 2014). It can also lower IL-6 (Belcaro et al., 2010; Zhou et al., 2011) and TNF-α levels (Aggarwal et al., 2013).

Limitations and Directions for Future Research

The relatively small samples size used in this study limits the reliability and statistical power associated with the findings. For evaluation of curcumin's antidepressant effects, data from approximately 50 participants was obtained. Sample sizes were even lower when evaluating the effects of curcumin on people with atypical depression. The results from this study therefore require replication with larger sample sizes.

In this study, a high proportion (approx. 70%) of participants reported a history of multiple depressive episodes, thereby reflecting a sample with high chronicity of depression and likely treatment resistance. Comparative evaluations of the efficacy of curcumin with single- and recurrent-episode depressives would be useful, along with an examination of the influence of differing treatment periods and curcumin dosages.

Investigations into the antidepressant effects of curcumin would also be strengthened by studies controlling for important covariates such as medication use, psychological therapies, medical illnesses and BMI. While this 8-week study now represents the longest investigation into effects of curcumin on depression, future investigations with longer follow up periods are certainly warranted. Because the effects of curcumin were not recognised until after week 4, longer treatment duration will be necessary to determine if mood improvements maintain or increase over time.

Self-report instruments were used to monitor changes in mood. While this provides a valid index of clinical progress, the implementation of additional measures, such as reliable and valid clinician-rated instruments, will provide a more robust evaluation of the clinical effectiveness of curcumin.

Other areas of interest include investigations into the optimal curcumin dose for best antidepressant effects and the frequency of intake. In two studies a dose of 500 mg twice daily has been used, and in the other 500 mg once daily was used. Because of problems with

bioavailability of curcumin, doses greater than these may be necessary to achieve optimal treatment efficacy. Increasing intake to 3 times a day may also be necessary to combat problems associated with the short half-life of curcumin (Anand et al., 2007).

In conclusion, the present findings provide partial support for the antidepressant effects of curcumin in people with major depressive disorder, and particularly atypical depression. However, replication with larger clinical trials, using variable doses, and conducted over an extended treatment period is required.

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Chapter 6:
The potential utility of peripheral biomarkers in major depression: its application in curcumin treatment

As reviewed in Chapter 4, while pharmaceutical and psychological treatments may influence several dysregulated biological pathways associated with depression, pre-treatment disturbances in these pathways can also be adversely associated with treatment resistance. In particular, certain levels of immuno-inflammatory and HPA biomarkers have been linked with treatment resistance to pharmaceutical and psychological therapies. Therefore, the use of biomarkers has the potential to predict treatment response, facilitate treatment matching, and thereby enhance treatment efficacy. Findings from studies examining peripheral markers associated with immuno-inflammation and oxidative stress in major depression are reviewed in the following published paper.

A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers

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Abstract

Biomarkers are regularly used in medicine to provide objective indicators of normal biological processes, pathogenic processes or pharmacological responses to therapeutic interventions, and have proved invaluable in expanding our understanding and treatment of medical diseases. In the field of psychiatry, assessment and treatment has, however, primarily relied on patient interviews and questionnaires for diagnostic and treatment purposes. Biomarkers in psychiatry present a promising addition to advance the diagnosis, treatment and prevention of psychiatric diseases. This review provides a summary on the potential of peripheral biomarkers in major depression with a specific emphasis on those related to inflammatory/immune and oxidative stress/antioxidant defences. The complexities associated with biomarker assessment are reviewed specifically around their collection, analysis and interpretation. Focus is placed on the potential of peripheral biomarkers to aid diagnosis, predict treatment response, enhance treatment-matching, and prevent the onset or relapse of major depression.

Abbreviations: 8-OHdG, 8-hydroxy-2-deoxyguanosine; 8-oxoGuo, 8-oxo-7,8-dihydroguanosine; BDNF, brain-derived neurotropic factor; BMI, body mass index; COX, cyclooxygenase; CRP, C-reactive protein; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECT, electroconvulsive therapy; ESR, erythrocytes sedimentation rate; F2-isoPM, 2,3-dinor-5,6-dihydro-15-F2t-isoprostane; GPx, glutathione peroxidase; GTP-CH1, GTP cyclohydrolase I; hs-CRP, high sensitivity CRP; IDO, indoleamine 2,3 dioxygenase; IFN, interferon; IL, interleukin; IL-2R, interleukin-2 receptor; KYN, kynurenine; KYNA, kynurenic acid; MDA, malondialdehyde; RA, rheumatoid arthritis; RBC, red blood cell; RNA, ribonucleoside; SOD, superoxide dismutase; SSRI, serotonin reuptake inhibitor; TNF, tumour necrosis factor; TRP, tryptophan; TRYCATs, tryptophan catabolites along the IDO pathway.

Introduction

Currently the diagnosis of major depression is carried out through a combination of patient interviews, checklists and self-report questionnaires. These generally rely on a list of symptoms derived from the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV) and now more recently, its revised 5th edition, DSM-5. Unfortunately, there is debate about the value and objectivity of this symptom-based assessment process (Hilsenroth, Baity, Mooney, & Meyer, 2004; Phillips et al., 2012; Stein et al., 2010) particularly around limitations associated with the development of personalised treatment plans.

Biomarkers are indicators of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention that can be measured and evaluated objectively (Biomarkers Definitions Working Group, 2001). They have the potential to overcome some of the issues associated with symptom-based assessments. In medical and pharmaceutical practice, biomarkers are regularly used to support the presence or absence of specific diseases (diagnostic biomarkers), predict optimal treatment options (treatment biomarkers), measure treatment progress (treatment-response biomarkers), and predict the onset of future disease (predictive biomarkers) (Boksa, 2013; Kluge, Alsaif, Guest, Schwarz, & Bahn, 2011; Schmidt, Shelton, & Duman, 2011). Unfortunately, progress in biomarker research on depression is hindered by the considerable heterogeneity associated with this disorder. While major depression comprises changes in sleep, appetite, weight, and psychomotor behaviour, these can involve both increases and decreases in symptoms. Complaints about the most debilitating depressive symptom or constellation of symptoms can also vary considerably across individuals. These include variations in the severity of fatigue, worthlessness, suicidal ideation, and effects on memory and concentration. Further complications include the high comorbidity between depression and other medical and

psychiatric conditions (Voinov, Richie, & Bailey, 2013), and factors associated with unique differences across gender, age, lifestyle and other mediating or triggering factors.

In this paper, many of the most commonly researched biomarkers in major depression are reviewed. Only peripheral biomarkers have been selected for review given their suitability and ease of collection in clinical practice. Furthermore, only biomarkers associated with inflammation/ immune response and oxidative stress/antioxidant defences have been selected for review as this is an area gaining momentum in depression research (Leonard & Maes, 2012; Maes, Leonard, et al., 2011; Raison & Miller, 2011).

Common oxidative and inflammatory biomarkers measured in depression studies

Several commonly-researched peripheral biomarkers in major depression are listed in Table 1, and pathways associated with their production are detailed in Figure 2. A brief description of each marker is provided, and they are categorised into inflammatory/immune response biomarkers and oxidative stress/antioxidant defence biomarkers. However, these markers are not mutually exclusive as they can greatly influence the production of other important biomarkers.

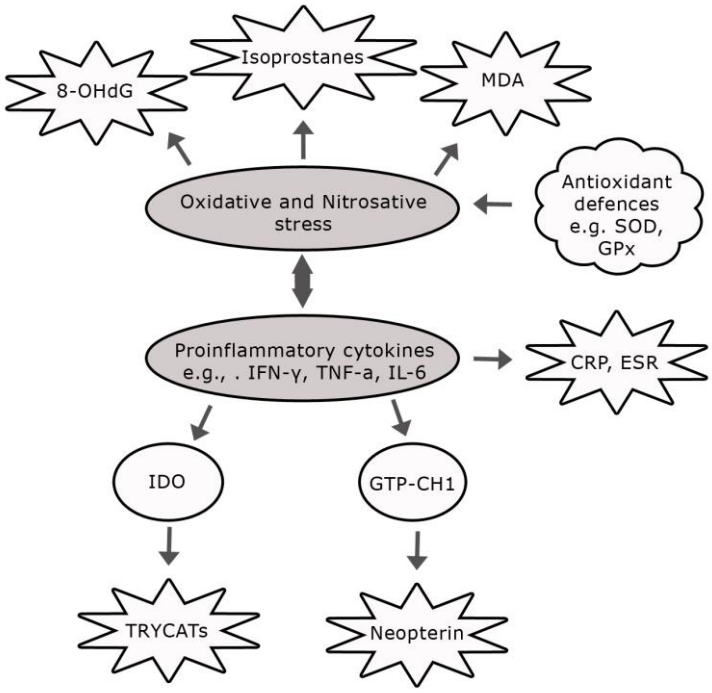

Figure 1. *Pathways associated with oxidative stress and inflammatory biomarkers in major depression.* Elevated pro-inflammatory cytokines (e.g, IL-6, TNF-α, and IFN-γ) upregulate the production of enzymes indoleamine 2,3 dioxygenase (IDO) and GTP cyclohydrolase I (GTP-CH1), leading to increased production of TRYCATs and neopterin, respectively. ESR and CRP are also markers of inflammation. Oxidative stress is influenced by antioxidant defence systems including the antioxidant enzymes SOD and GPx. Elevated oxidative stress may lead to a greater production of OHdG, MDA and isoprostanes. A bidirectional relationship exists between inflammation and oxidative stress, up- or down-regulating each other's production.

Table 1. Common peripheral biomarkers measured in studies on major depression

Inflammation and immune response peripheral biomarkers	
C-reactive protein (CRP)	An acute-phase protein found in the blood that rises in response to inflammation.
Cytokines	Immuno-modulating proteins, peptides, or glycoproteins (e.g., interleukins and interferons) secreted by specific cells of the immune system, which carry signals locally between cells, and have an effect on target cells. Cytokines are generally classified by their ability to promote or inhibit inflammatory responses and the type of T-lymphocytes with which they are associated (termed Th1, Th2, and Th17).
Neopterin	Released by macrophages and considered a marker of cell-mediated inflammation activation.
Erythrocyte sedimentation rate (ESR)	A non-specific index of inflammation which measures the rate at which red blood cells sediment in a period of one hour.
TRYCATs (tryptophan catabolites along the IDO pathway)	Production of TRYCATs such as kynurenine, kynurenic acid, xanthurenic acid, and quinolinic acid, may be increased following immune activation. An immune response induces indoleamine-(2,3)-dioxygenase (IDO), an enzyme which degrades tryptophan down the TRYCAT pathway, summarised in Figure 1.
Oxidative stress and antioxidant defence peripheral biomarkers	
Malondialdehyde (MDA)	Product of chemical damage caused by oxygen free radicals to the lipid component of cell membranes.
8-hydroxy-2-deoxyguanosine (8-OHdG)	A repair product of the oxidation of guanine in DNA, can be used to estimate the rate of oxidative DNA damage.
Isoprostanes	Prostaglandin-like compounds produced by non-enzymatic peroxidation of arachidonic acid.
Superoxide dismutases (SOD)	Important antioxidant defence in nearly all cells exposed to oxygen. Enzymes that catalyse the dismutation of superoxide into oxygen and hydrogen peroxide.
Glutathione peroxidase (GPx)	Enzyme that catalyses the reduction of hydroxyperoxides by glutathione. Main function is to protect against the damaging effect of endogenously formed hydroxyperoxides.
Glutathione reductase	Important cellular antioxidant enzyme that reduces glutathione disulfide (GSSG) to the sulfhydryl form glutathione.
Reduced glutathione	Measure of glutathione status.

A summary of potential diagnostic biomarkers in depression

Biomarkers may be used to assist clinical diagnosis. From a diagnostic perspective, their value is largely dependent on their ability to identify the presence (sensitivity) or absence (specificity) of disease. While these biomarkers are reviewed individually, it is likely that a combination of biomarkers will be required to increase sensitivity and specificity rates to levels required for diagnostic purposes (Schmidt, et al., 2011).

Inflammation and immune response biomarkers

C-reactive protein (CRP) – findings from meta-analyses have confirmed that major depression is associated with increased CRP levels (Howren, Lamkin, & Suls, 2009; Valkanova, Ebmeier, & Allan, 2013). In a recent meta-analysis on longitudinal studies by Valkanova et al. (2013) it was also established that raised CRP levels were associated with an increased risk of subsequent depression. However, these findings are not uniform and in subgroup analyses, elevated CRP was associated with atypical depression (Hickman, Khambaty, & Stewart, 2013), somatic symptoms (Duivis, Vogelzangs, Kupper, de Jonge, & Penninx, 2013), depressed men with an older age of depression onset (Vogelzangs et al., 2012), depressed men in general (Elovainio et al., 2009; Ford & Erlinger, 2004; Liukkonen et al., 2011), depressed patients with a greater history of childhood adversity (Miller & Cole, 2012), and cumulative depressive episodes (Copeland, Shanahan, Worthman, Angold, & Costello, 2012).

High sensitivity CRP (hs-CRP) assays are a more sensitive measure of inflammation, having a range of measurement that extends below that typical of most conventional CRP assays. Investigations into the link between hs-CRP and depression are continuing, and on the whole provide further support for their relationship (Luukinen, Jokelainen, & Hedberg, 2010; Ma et al., 2010; Pasco et al., 2010).

Cytokines - along with research on CRP levels, cytokine profiles in patients with major depression are the most commonly measured immune biomarkers. In recent meta-analyses, disturbed cytokine profiles have been confirmed in patients with major depression. Significantly higher concentrations of tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were identified in a meta-analysis by Dowlati et al. (2010); and in a meta-analysis on community and clinical populations, elevated IL-1 and IL-6 were positively associated with depression (Howren, et al., 2009). Greater elevations in IL-6 were found in subgroups where depressive disorders were formally diagnosed, as opposed to a diagnosis made using standardised inventories. Populations obtained from inpatient and outpatient settings also had higher IL-6 levels compared to the general community (Hiles, Baker, de Malmanche, & Attia, 2012b). In a meta-analysis by Liu et al. (2012), elevated blood levels of soluble interleukin-2 receptor (sIL-2R), TNF-α and IL-6 in patients with depression were demonstrated, although effect sizes were significantly influenced by the composition of the blood sample. Specifically, differences in sIL-2R and IL-6 were significant both in plasma and serum, whereas TNF-α was significantly different from healthy controls only when it was measured via serum. Finally, in a systematic review and meta-analysis on longitudinal studies, IL-6 was associated with depressive symptoms, although after considering only correlations adjusted for confounding variables such as smoking, alcohol consumption, body-mass index, cholesterol level, physical activity, medication use or chronic illness, the relationship became statistically non-significant (Valkanova, et al., 2013).

Neopterin – levels of plasma neopterin are increased in depressed patients (Celik et al., 2010; Maes et al., 2013; Maes et al., 1994; Maes, Twisk, & Ringel, 2012; Rybka et al., 2013) and particularly in patients suffering from melancholic symptoms (Maes, Mihaylova, Kubera, & Ringel, 2012; Maes, et al., 1994). Greater concentrations of neopterin were also reported in

patients suffering from two or more episodes of depression compared to first-episode populations (Celik, et al., 2010). Nevertheless, differences in concentrations of neopterin between depressed and healthy samples have not been identified in some studies (Hoekstra et al., 2001; O'Toole, Chiappelli, & Rubin, 1998).

Erythrocyte sedimentation rate (ESR) – higher ESR was identified in depressed patients compared to healthy volunteers (Chavda, Kantharia, & Jaykaran, 2011), and in depressed smokers compared to non-depressed, never smokers (Vargas et al., 2013). ESR was also elevated in rheumatoid arthritis (RA) patients suffering from depression compared to non-depressed RA sufferers (Abdel-Nasser et al., 1998).

TRYCATs – The TRYCATs pathway is shown in Figure 2, and a summary of studies examining the relationship between depression and various TRYCAT analytes is provided in Table 2. In general, depression is associated with lowered tryptophan (TRP), increased indoleamine-2,3-dioxygenase (IDO) activity and reduced levels of the neuroprotective TRYCAT, kynurenic acid (KYNA). However, this is not uniform (Gabbay et al., 2010; Maes, Galecki, Verkerk, & Rief, 2011; Maes & Rief, 2012), indicating that increased TRYCAT activity may be related to specific subtypes of depression or depressive symptoms. IDO activity is increased in patients suffering from somatisation (Maes, Galecki, et al., 2011; Maes & Rief, 2012), depressed patients with a history of suicide attempts (Sublette et al., 2011) and adolescents with depression and melancholic symptoms (Gabbay, et al., 2010).

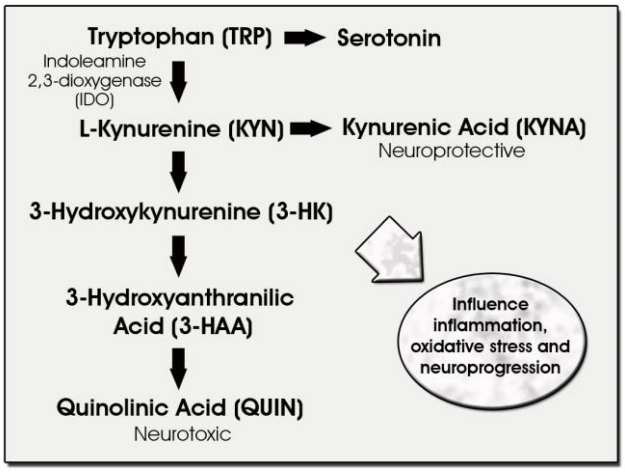

Figure 2. *TRYCATs pathway.* The TRYCATs pathway starts with the degradation of tryptophan by the enzyme, indoleamine 2,3-dioxygenase (IDO) which is upregulated by pro-inflammatory cytokines (e.g. IFN-γ, TNF-α, IL-, IL-6). These TRYCATS have neuroprotective and neurotoxic effects on the CNS and influence monoaminergic transmission.

Table 2. *Summary of TRYCAT depression studies.* Elevated KYN and KYN/TRP indicates greater IDO activity. Elevated KYNA and KYNA/KYN ratio indicates greater neuroprotection.

Population	**Sample used**	**Tryptophan**	**IDO activity**		**Neuroprotection**		
			KYN	**KYN/TRP Ratio**	**KYNA**	**KYNA/KYN ratio**	**Reference**
Healthy pregnant women	Morning plasma after overnight fast	No correlation with depression or anxiety postpartum	Positively correlated with depression and anxiety postpartum	Positively correlated with depression and anxiety postpartum			Maes et al. (2002)
Depressed patients; healthy controls	Morning plasma after overnight fast	No difference between depressed and controls	No difference	↑ in depressed than controls	↓ in depressed than controls	↓ in depressed than controls	Myint et al. (2007)
Women high risk for postpartum depression	Serum; time of collection not specified	Negatively correlated with total depression score in the prepartum period, but not in other time periods.	Not correlated with depressive symptoms over time	Not correlated with depressive symptoms over time			Scrandis et al. (2008)
Patients with coronary artery disease	Morning plasma after overnight fast	No correlation with depression scores		Positively correlated with depression scores			Swardfager et al. (2009)
Depressed adolescents with melancholic features; non-melancholic depressed adolescents; healthy controls	Morning plasma after overnight fast	↓ in melancholic than controls and non-melancholic.	No difference between all groups	↑ in melancholic than controls and non-melancholic			Gabbay et al. (2010)

Population	Sample used	Tryptophan	IDO activity		Neuroprotection		
			KYN	KYN/TRP Ratio	KYNA	KYNA/KYN ratio	Reference
Normal controls (NC); patients with somatization (SOM); patients with depression (DEP); patients with comorbid somatization and depression (SOM+DEP)	Morning plasma after overnight fast	↓ SOM compared to SOM+MDD, MDD and HC; No difference between SOM+MDD and MDD; ↓ SOM+MDD and MDD than HC.	↓ SOM and SOM+DEP than NC.	↑ SOM than SOM+MDD and NC; no difference between SOM and MDD or MDD versus NC.	↓ SOM and SOM+MDD than MDD and NC; ↓ MDD to NC.	↓ SOM than MDD and NC; ↓ SOM+MDD than MDD and NC; no difference between MDD and NC.	Maes et al. (2011)
Depressed patients; healthy volunteers	Plasma; Time of collection not specified	↑ in suicide attempters than non-attempters; No difference between depressed and controls	No difference between depressed and controls; ↑ in suicide attempters than non-attempters	↑ in depressed than controls			Sublette et al. (2011)
Depressed patients; healthy controls	Plasma collected in early afternoon	↓ in depressed than controls	No difference between groups	↑ in depressed than controls	No difference between groups	↑ in depressed than controls	Hughes et al. (2012)
Normal controls (NC); patients with somatization (SOM); patients with depression (DEP); patients with comorbid somatization and depression (SOM+DEP)	Morning plasma after overnight fast	↓ SOM than all other groups; no difference in SOM+DEP and DEP. No difference between SOM+DEP and DEP; ↓ in SOM+DEP and DEP than HC		↑ SOM than in NC.		↓ SOM and SOM+DEP than in DEP and NC.	Maes and Rief (2012)
Depressed inpatients; healthy controls	Morning serum after overnight fast	↓ depressed than controls	↑ in depressed than controls	↑ in depressed than controls			Myint et al (2013)

Oxidative stress and antioxidant defence biomarkers

Malondialdehyde (MDA) – MDA concentrations in depressed patients are by-and-large increased compared to healthy control groups (Bilici et al., 2001; Galecki, Szemraj, Bienkiewicz, Florkowski, & Galecka, 2009; Khanzode, Dakhale, Khanzode, Saoji, & Palasodkar, 2003; Kotan, Sarandol, Kirhan, Ozkaya, & Kirli, 2011; Ozcan, Gulec, Ozerol, Polat, & Akyol, 2004; Sarandol et al., 2007). Elevated levels of MDA have also been identified in patients diagnosed with recurrent depressive disorder (Rybka, et al., 2013), and concentrations are even greater in depressed patients with a history of recurrent episodes of depression compared to patients suffering from their first episode (Stefanescu & Ciobica, 2012). Elevated MDA levels have also been confirmed in depressed patients suffering from chronic heart failure (Michalakeas et al., 2011) and newly diagnosed gastric adenocarcinoma (Wei et al., 2009).

8-hydroxy-2-deoxyguanosine (8-OHdG) –an association between depression and levels of 8-OHdG has been confirmed in several cross-sectional studies. Compared to a healthy comparison group, urinary (Maes et al., 2009) and serum (Forlenza & Miller, 2006) levels of 8-OHdG were greater in people suffering from major depression. Levels of 8-OHdG also correlated positively with the severity of depression (Forlenza & Miller, 2006; Jorgensen et al., 2013), and participants with recurrent episodes of depression had higher levels than those with single episodes (Forlenza & Miller, 2006). While no differences in urinary 8-OHdG were identified between depressed and healthy samples, its ribonucleoside (RNA) analogue, 8-oxo-7,8-dihydroguanosine (8-oxoGuo), was higher in depressed patients, particularly those suffering from severe depression (Jorgensen, et al., 2013). Increased 8-OHdG may be a characteristic of clinically-diagnosed depression, as no differences were found in community-based populations suffering from depressive symptoms (Iida et al., 2011; Yi et al., 2012).

Isoprostanes – levels of isoprostanes are elevated in patients suffering from depression as demonstrated by higher urinary concentrations of 8-iso-PGF2α (Chung, Schmidt, Stein, Morrow, & Salomon, 2013; Milaneschi et al., 2013), and a β-oxidation metabolite of 8-iso-PGF2α, 2,3-dinor-5,6-dihydro-15-F_{2t}-isoprostane (F2-isoPM). It is important to note that Milaneschi et al. (2013) found this association in men but not women. Elevated serum (Yager, Forlenza, & Miller, 2010) and plasma (Dimopoulos, Piperi, Psarra, Lea, & Kalofoutis, 2008) 8-iso-PGF2α, concentrations were also found in depressed populations compared to a healthy comparison group.

Superoxide dismutase (SOD) – disturbances in SOD activity are generally found in depressed populations. However, findings are inconsistent in the direction of this disturbance. For example, decreased red blood cell (RBC) SOD activity was reported in patients diagnosed with recurrent depressive disorder (Rybka, et al., 2013), lowered serum SOD levels in patients with major depression (Herken et al., 2007; Stefanescu & Ciobica, 2012), and even greater reductions in serum SOD in patients with recurrent depression, compared to a first episode group (Stefanescu & Ciobica, 2012). However, in other studies increased RBC SOD in depressed patients were found (Bilici, et al., 2001; Galecki, Szemraj, Bienkiewicz, Florkowski, et al., 2009; Kodydkova et al., 2009; Kotan, et al., 2011; Sarandol, et al., 2007), and serum SOD was positively associated with increasing severity of depression (Khanzode, et al., 2003). Reasons for these inconsistent findings are not clear, although may be related to variable collection protocols, analysis methods and whether RBC or serum was analysed (e.g., RBC levels were elevated in four out of five studies reviewed, while serum levels were lower in two out of three studies reviewed). Differences in the characteristics of depressed populations sampled may also be important as severity (Khanzode, et al., 2003) and length of depression (Stefanescu & Ciobica, 2012) are important factors influencing SOD activity.

Glutathione –As shown in Table 3, conclusions regarding glutathione activity are difficult as findings have been inconsistent and often dependent on the glutathione measure used and type of specimen evaluated. Levels of RBC glutathione peroxidase (GPx) have been most commonly evaluated in depressed populations with decreases (Kodydkova, et al., 2009; Rybka, et al., 2013), increases (Bilici, et al., 2001), and no differences (Galecki, Szemraj, Bienkiewicz, Florkowski, et al., 2009) found between depressed and healthy control groups.

Table 3. *Summary of studies investigating glutathione status in major depression.*

Glutathione measure	Direction of change compared to controls	Study
Glutathione peroxidase	↓ RBC	Rybka et al., (2013)
	↓ RBC	Kodydkova et al., (2009)
	↑ RBC	Bilici et al., (2001)
	= RBC	Galecki et al., (2009)
	↓ whole blood	Maes et al., (2011)
	= whole blood	Kotan et al., (2011)
	= plasma	Bilici et al., (2001)
	↓ serum in recurrent depression	Stefanescu & Ciobica (2012)
Glutathione reductase	= RBC	Rybka et al. (2013)
	= RBC	Bilici et al., (2001)
	↑ plasma	Bilici et al., (2001)
Reduced glutathione	↓ whole blood	Rybka et al. (2013)

(↑) increased (↓) decreased or (=) no change compared to controls

Biomarkers associated with the treatment of depression

The potential of biomarkers as a measure of treatment response

Measures of treatment progress over time are provided by treatment-response biomarkers. Currently, assessment of treatment progress in major depression is undertaken in clinical practice through clinical interviews, and to a lesser extent questionnaires and inventories. With validation of treatment-response biomarkers, further data about treatment efficacy may also be obtained by monitoring changes in biomarker levels over time.

CRP – in a meta-analysis of eight studies investigating the effects of antidepressant treatment on CRP levels it was concluded that antidepressant medication (particularly selective serotonin reuptake inhibitors, SSRIs) marginally lowered levels of CRP (Hiles, Baker, de Malmanche, & Attia, 2012a). However, in a meta-regression in this review, no significant association between baseline CRP and change in depressive symptoms was identified. Moreover, a trend was noted where higher baseline CRP was associated with larger decreases in depressive symptoms.

Cytokines – in a meta-analysis by Hannestad et al. (2011), antidepressant treatment was found to lower levels of IL-1β and possibly IL-6, but had no effect on TNF-α. In a further analysis of antidepressant classes, SSRIs lowered levels of IL-6 and TNFα (Hannestad, et al., 2011). In a separate meta-analysis, it was confirmed that antidepressants lowered levels of IL-6 and non-significantly decreased levels of IL-10. A pattern was also identified where higher baseline IL-6 was associated with larger decreases in depressive symptoms (Hiles, et al., 2012a).

Electroconvulsive therapy (ECT) also influences cytokine profiles in depressed patients. ECT increased IL-1β and IL-6 at 3- and 6-hour time points after treatment (Lehtimaki et al., 2008). Hestad et al. (2003) demonstrated that the clinical improvement during repeated ECT was accompanied by a gradual and significant decline in TNF-α, reaching levels comparable with those in healthy controls at the end of the study. Such a decline was not seen in depressed patients not receiving ECT, who instead showed elevated TNF-α levels throughout the study period.

Neopterin – a course of treatment with ECT significantly elevated neopterin levels in depressed responders but these levels did not change in non-responders (Hoekstra, et al.,

2001). Anderson et al. (1992) found that a positive therapeutic response was associated with a reduced neopterin:biopterin ratio in patients with psychotic depression treated with ECT.

Malondialdehyde (MDA) –changes in MDA levels following treatment with antidepressant medication are largely associated with reduced concentrations and a return to normal levels in patients recovering from major depression. After three months of treatment with SSRIs, MDA was reduced to levels similar to a healthy comparison group (Bilici, et al., 2001; Khanzode, et al., 2003). Reductions in MDA were also observed in first-episode depressive patients who achieved remission following three months of treatment with fluoxetine (Galecki, Szemraj, Bienkiewicz, Florkowski, et al., 2009). MDA also decreased significantly following 24 weeks of antidepressant treatment (Kotan, et al., 2011); however, no such change was observed after a shorter treatment period of 6 weeks (Sarandol, et al., 2007).

8-hydroxy-2-deoxyguanosine (8-OHdG) – a single study was identified examining changes in 8-OHdG following psychiatric treatment. Jorgensen et al. (2013) found no change in 8-OHdG levels following ECT although its RNA analogue, 8-oxoGuo, increased significantly.

Isoprostanes –the effect of antidepressant treatment on isoprostane levels has been investigated in one study. Excretion of F2 isoprostanes increased significantly following 8 weeks of treatment with bupropion or sertraline in patients with major depression. The researchers also found that increases in F2 isoprostane were associated with improvement in depression severity (Chung, et al., 2013).

Superoxide dismutase – research on the effect of antidepressant medication on SOD activity has been inconsistent. RBC SOD activity was lowered following treatment with different classes of antidepressants after 24 weeks, although no change was noted after 6 or 12 weeks (Kotan, et al., 2011). Serum SOD activity was lowered following 8 weeks of SSRI administration (Khanzode, et al., 2003), and RBC SOD was reduced after 3 months of

treatment with several antidepressant classes (Bilici, et al., 2001). In contrast to these findings, no significant change in RBC SOD was observed in patients after 3 months of treatment with fluoxetine (Galecki, Szemraj, Bienkiewicz, Florkowski, et al., 2009; Galecki, Szemraj, Bienkiewicz, Zboralski, & Galecka, 2009), or in patients following 6 weeks of treatment with several antidepressant classes (Bilici, et al., 2001). Further disparity in findings is demonstrated by Herken et al., (2007) where 8 weeks of SSRI treatment was associated with increased serum SOD levels. Unique to this study was the observation that baseline SOD levels were lowered (rather than elevated) in the depressed population compared to the control group.

In sum, the effect of antidepressant medication on SOD activity is not clear. These inconsistent findings may be attributed to the varying antioxidant effects of different antidepressant classes, or to differences in the depressed populations studied, as SOD activity is influenced by the number of depressive episodes (Stefanescu & Ciobica, 2012) and severity of depression (Khanzode, et al., 2003). Blood samples used in the studies (e.g., serum or RBC) and the length of antidepressant treatment may also be important factors influencing findings.

Glutathione activity - No change in GPx was observed after three months of treatment with fluoxetine (Galecki, Szemraj, Bienkiewicz, Florkowski, et al., 2009) or 24 weeks of antidepressant treatment (Kotan, et al., 2011). Galecki et al. (2009) found that the addition of acetylsalicylic acid to fluoxetine treatment provided no additional benefit to treatment efficacy, although it was able to lower GPx activity after 3 months. Plasma glutathione reductase and glutathione peroxidase decreased after 3 months of treatment with SSRIs (Bilici, et al., 2001).

TRYCATs - Little or no change was observed in the concentrations of any of the TRYCATs following treatment with fluoxetine, fluoxetine plus the thyroid hormone triiodothyronine

(T3), or counselling (Mackay et al., 2009). Despite this, in a correlation analysis at weeks 6 and 18, highly significant relationships between several of the TRYCATs and psychiatric inventory scores were revealed. In patients treated with fluoxetine or fluoxetine and T3, positive correlations were observed between psychiatric rating scores and concentrations of tryptophan and some TRYCATs, such as kynurenic acid and 3-hydroxyanthranilic acid. That is, increased levels of some TRYCATs were associated with increased psychiatric severity. Myint et al. (2007) found no changes in the TRYCATs, kynurenine, kynurenic acid and tryptophan, and related ratios after 6 weeks of antidepressant treatment. The neuroprotective ratio of patients with their first episode of depression increased significantly after treatment, but this did not correlate with changes in depression severity.

Overall, the studies reviewed above suggest that treatments for depression (particularly antidepressant medication and ECT) influence oxidative stress and inflammatory markers. Unfortunately, investigations into the significance of such findings are still in their infancy. In the majority of studies the relationship between biomarker variations and changes in depressive symptoms has not been examined, making conclusions about the value of biomarker evaluations as a measure of treatment success difficult. Where studies have investigated this relationship, findings have been inconsistent. Moreover, the mechanisms underlying biomarker variation are unknown. While the treatments *per se* may improve inflammatory and oxidative stress pathways, it is also possible that improved mood resulting from successful treatment could lead to cognitive, behavioural and lifestyle changes (e.g., increased exercise, improved diet, positive outlook, improved sleep) that may be responsible for the changes observed in biomarkers. Further research in this area is required.

The potential of biomarkers for enhancing treatment matching

The potential of inflammatory and oxidative stress biomarkers to facilitate treatment matching and, in turn, enhance treatment efficacy has been examined in only a few studies. From a theoretical standpoint, assessment of pre-treatment biomarkers has the potential to enhance clinical decision-making by enabling clinicians to choose the most appropriate treatment for a specific individual or group of individuals. Monitoring changes in biomarkers following treatment may also provide an indication of the likelihood of treatment success.

In a study by Raison et al. (2013), infliximab, a TNF antagonist, was administered (via infusion) to patients with major depression. When the depressed group was examined as a whole, infliximab was no more effective than placebo. However, in patients with a baseline hs-CRP greater than 5 mg/L, a significantly greater treatment response was observed in infliximab-treated patients compared to placebo. Additionally, Change et al. (2012) found that baseline CRP levels correlated significantly with the response to antidepressant treatment at week 2. However, in patients with comorbid coronary heart disease and depression treated with antidepressants, baseline levels of hs-CRP were not associated with 10-week post-treatment depression scores (Bot et al., 2011).

The potential of biomarkers to predict the onset of depression

Preventative-based efforts hold significant promise in reducing the prevalence of depression and other psychiatric disorders in the general community. Currently several psychological, lifestyle, social and physical factors are known to be associated with an increased risk of developing major depression or relapsing after a period of remission. Measurement of biomarkers presents an additional option for risk factor identification, further enabling decision making around early identification, treatment and relapse prevention.

Research into the predictive potential of inflammatory and oxidative stress markers is still in its early stages. However, in a prospective analysis, increasing CRP levels were associated with increasing risk for hospitalisation with depression (Wium-Andersen, Orsted, Nielsen, & Nordestgaard, 2013). Greater CRP levels were also identified as an independent risk marker for *de novo* depression in women (Pasco, et al., 2010). Liukkonen et al. (2006) also found a four-fold increase in the likelihood of recurrent depression in men with a hs-CRP level greater than 3 mg/L, although no such association was identified in women. In a meta-analysis of longitudinal studies, raised CRP, and to a lesser extent IL-6, was associated with an increased risk of subsequent depressive symptoms (Valkanova, et al., 2013). In a study on people undergoing IFN-α treatment for hepatitis C, kynurenic acid levels were positively associated with an increased risk of the development of depression (Wichers et al., 2005).

Complexities in biomarker identification

The clinical utility of biomarkers in psychiatry is still in its infancy. Although biomarker measurement has the potential to be an exciting addition to psychiatric assessment, it is associated with numerous complexities. As demonstrated in this review, a number of inflammatory and oxidative stress biomarkers are associated with depression. However, none of these has sufficient sensitivity and specificity to be used in isolation. This signifies that further research is required to identify alternative, more suitable single or collective biomarkers. However, results have also been hampered by numerous inconsistencies and challenges across studies.

Inconsistencies in specimen collection are a serious drawback in research. Typically, blood, urine and saliva samples are collected in research studies. Within blood collections, plasma, serum, red blood cells, and whole blood are additional options for biomarker measurement. A major drawback associated with the studies reviewed above relates to variation in the

specimens utilised to make comparisons. This may at least partly account for the inconsistent findings across studies. Further research is required to determine the most appropriate and accurate specimen to be utilised in research and clinical practice.

A related problem refers to inconsistency in collection, storage and measurement protocols. While the majority of studies utilised morning, fasting collections, this was not always the case. Protocols used to measure biomarkers also often lacked consistency as did storage conditions following collection. Further research is required to determine the most accurate collection, storage and measurement protocols. Such protocols also need to be cost-effective and easily applied in clinical settings.

A greater understanding of patient variables such as age, sex, medication use, menstrual cycle and status, time of day, smoking status and BMI are also crucial factors to consider in protocol development (Codoner-Franch et al., 2012; Hrboticky, Leiter, & Anderson, 1989; Rosello-Lleti et al., 2012; Theofylaktopoulou et al., 2013). Although depression is associated with several inflammatory and oxidative stress biomarkers, confounding variables need to be accounted for. For example, despite CRP being commonly used as a marker of inflammation and cardiovascular disease, levels may be influenced by time of day (Koc, Karaarslan, Abali, & Batur, 2010; Rudnicka, Rumley, Lowe, & Strachan, 2007), gender (Khera et al., 2005; Lakoski et al., 2006), age (Shanahan et al., 2013; Woloshin & Schwartz, 2005), menstrual cycle (Gaskins et al., 2012; Wander, Brindle, & O'Connor, 2008), and BMI (Choi, Joseph, & Pilote, 2013). These factors will impact on the reliability of conclusions made and require consideration in hypothesis generation. Some of these problems may be overcome by establishing subgroup normative data (e.g., based on age and gender) for the varying markers discussed.

Inconsistencies in patient populations used in research also present another serious problem. Major depression is a heterogeneous disorder, thereby making generalised

conclusions difficult. There is a need for investigation into biomarkers associated with specific depression subtypes, categories or even specific symptoms. Atypical, melancholic, suicidal, and somatic-dominant are examples of some 'depression subtypes' that have revealed differing biomarker profiles. The specificity and sensitivity of biomarkers may increase following examination of well-defined groups.

The effect of treating depression on biomarkers has primarily focused on antidepressant medication and ECT. Research into other treatments such as psychological therapies and lifestyle interventions (e.g., sleep, diet and exercise) is lacking. The influence of more targeted anti-inflammatory treatments and antioxidant therapies on depressive symptoms and biomarker levels are also required. It seems logical that if oxidative stress or inflammation is dysregulated in an individual or a population group, then treatments targeting this dysregulation should be utilised. Preliminary research into anti-inflammatory medication has begun with some positive initial findings (Muller, Myint, & Schwarz, 2011). However, as recently determined by Raison et al. (2013), treatment with infliximab, a TNF antagonist, was effective only for individuals with high levels of CRP. Other potential treatment candidates include COX-2 inhibitors (Muller, et al., 2011), immune-modulating and antioxidant herbs and spices such as curcumin (A. L. Lopresti, Hood, & Drummond, 2012) and green tea (Cabrera, Artacho, & Gimenez, 2006; Rietveld & Wiseman, 2003), and the large array of antioxidant nutrients such as coenzyme Q_{10}, zinc, vitamin C, vitamin E and n-acetylcysteine (Ng, Berk, Dean, & Bush, 2008; Zhang & Yao, 2013). Further investigation into the effects of specific antidepressant medications on inflammatory and oxidative stress markers may also facilitate better treatment matching.

Finally, while a limited selection of more commonly assessed biomarkers in depression research, specifically targeting inflammation and oxidative stress, have been covered in this

review, there remains an array of other potential options. These include measurements of amino acid levels, which are the precursors to neurotransmitters; markers of neurogenesis such as brain-derived neurotrophic factor; neurotransmitter metabolites such as 5-hydroxyindoleacetate, vanilmandelate and homovanillate (measures of serotonin, noradrenaline and dopamine respectively); growth factors such as insulin-like growth factor-1 and vascular endothelial growth factor; endocrine markers such as cortisol; measures of individual antioxidant levels such as zinc, coenzyme Q_{10}, selenium and collective antioxidant measures such as total antioxidant capacity; markers of nitrosative stress such as conjugated nitric-oxide (NO) adducts, - NO-tryptophan, NO-tyrosine, NO-arginine, and NO-cysteinyl; and genetic polymorphisms associated with serotonin and dopamine transporters and receptors.

Before biomarkers for depression can introduced into clinical practice, substantially greater research is required. Major depression is a common mental disorder with current treatment remission rates reaching only 20 to 40% (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). The addition of biomarkers has the potential to advance a more personalised treatment approach and enhance treatment efficacy.

Contributors:

Adrian Lopresti conducted a literature search and wrote the first draft of this manuscript. Peter Drummond, Garth Maker and Sean Hood reviewed the manuscript and provided feedback, corrections and recommendations on further drafts of this manuscript. All authors contributed to and have approved the final manuscript.

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As detailed in the previous paper, the use of peripheral biomarkers has the potential to predict treatment response and facilitate treatment matching. However, they have been greatly under-utilised in major depression. The potential of peripheral biomarkers was therefore examined in a study investigating the antidepressant effects of curcumin in people with major depression. It was hypothesised that:

1. The antidepressant mechanisms associated with curcumin can be evaluated through pre- and post-collections of peripheral biomarkers.
2. Curcumin will have greater antidepressant efficacy for specific subgroups of individuals with major depressive disorder. These subgroups can be identified through baseline biomarker concentrations which may facilitate treatment matching and therefore increase treatment success.

Curcumin and major depression: peripheral biomarkers to predict treatment response and antidepressant mechanisms of change

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Lopresti, A.L., et al. (2014) Curcumin and major depression: peripheral biomarkers to predict treatment response and antidepressant mechanisms of change (submitted for publication)

Abstract

In a recent randomised, double-blind, placebo controlled study conducted by our research group, supplementation with curcumin (500mg, twice daily) for 8 weeks was effective in reducing depressive symptoms in people with major depressive disorder. In the present study, the potential antidepressant mechanisms of action of curcumin were investigated by measuring several biomarkers in saliva, urine and blood at baseline and post-treatment. Samples were provided by 50 participants diagnosed with major depressive disorder, and the Inventory of Depressive Symptomatology self-rated version (IDS-SR_{30}) was used as the primary depression outcome measure. Compared to placebo, 8 weeks of curcumin supplementation was associated with elevations in urinary thromboxane B2 ($F_{1,19}$ = 8.21, p = .010) and substance P ($F_{1,19}$ = 5.59, p = .029). Higher baseline plasma endothelin-1 (rs = -.585; p = .004) and leptin (rs = -.451; p = .040) in curcumin-treated individuals was associated with greater reductions in IDS-SR_{30} score after 8 weeks of treatment. Reductions in plasma leptin concentrations were also associated with reductions in depressive symptoms (rs =.515; p = .024). A further exploratory analysis revealed that in participants with a high baseline endothelin-1, curcumin was more effective than placebo in reducing depressive symptoms ($F_{2,30}$ = 3.82, p = .033; Cohen's d = 1.26). Our findings demonstrate that curcumin supplementation influences several biomarkers that may be associated with its antidepressant mechanisms of action. Plasma concentrations of leptin and endothelin-1 seem to have particular relevance to treatment outcome. Further investigations using larger samples sizes are required to elucidate these findings.

Introduction

In medical and pharmaceutical practice biomarkers are regularly used to assist in the prediction, diagnosis and evaluation of treatments associated with disease (Biomarkers Definitions Working Group, 2001). However, in psychiatry, biomarkers are utilised primarily for research purposes and are seldom used in clinical practice. Greater understanding of biomarkers in psychiatry has the potential to enhance diagnostic accuracy, improve treatment-matching and evaluate treatment progress. Evaluation of biomarkers can also expand understanding into the mechanisms of change associated with specific treatments for depression (Adrian L. Lopresti, Maker, Hood, & Drummond, 2014).

Several dysregulated biological pathways have been identified in major depressive disorder including disturbances in monoaminergic activity, immuno-inflammation, oxidative stress, hypothalamus-pituitary-adrenal (HPA) activity and neuroprogression (Leonard & Maes, 2012). Examination of biomarkers is particularly relevant as there are identified differences between depressed and healthy populations in markers of immuno-inflammation, such as C-reactive protein, interleukin-6 and tumor-necrosis factor-α (Elomaa et al., 2012; Howren, et al., 2009); markers of oxidative stress such as malondialdehyde (MDA) (Galecki, Szemraj, Bienkiewicz, Florkowski, et al., 2009) and 8-Hydroxy-2-deoxyguanosine (8-OHdG) (Maes, et al., 2009); and markers of HPA activity such as increased baseline or post-dexamethasone cortisol (Belvederi Murri et al., 2014).

Because of its effects on all of these pathways, interest in curcumin for the treatment of major depression has increased. In animal models of depression, curcumin has demonstrated antidepressant and anxiolytic effects (A. L. Lopresti, et al., 2012). Three human-based trials on people with major depressive disorder have now been completed. In one study the addition of curcumin to antidepressant treatment provided no additional antidepressant benefit

(Bergman et al., 2013), whereas in another study curcumin had similar antidepressant efficacy to fluoxetine (Sanmukhani et al., 2014). However, in this latter study there was no placebo-control or blinding of participants from treatment conditions. In a recent randomised, double-blind, placebo controlled study conducted by our research team, curcumin was more effective than placebo in reducing depressive symptoms in people with major depression and was particularly effective in a subset of participants with atypical depression (A. L. Lopresti, Maes, Hood, Maker, & Drummond, 2014). In the present paper, exploratory analysis of results from this study is provided with an emphasis on the effects of curcumin on blood, urinary and salivary biomarkers, and on the potential of biomarkers to predict treatment response. The primary purpose of this analysis was to identify potentially important biomarkers that will require validation in future, greater powered studies.

Experimental Procedures

Study design

Details of this study have been previously published in Lopresti *et al.* (2014). Briefly, this study was an 8-week, randomised, double-blind, placebo-controlled clinical trial (Figure 1). The trial protocol was approved by the Human Research Ethics Committee at Murdoch University, Western Australia and was registered with the Australian New Zealand Clinical Trials Registry (no. 12612001260819). Participants were randomly and equally allocated into two groups (placebo and curcumin). Both curcumin and placebo capsules were packed in identical containers labelled by participant code numbers and were allocated according to order of participant enrolment in the study.

Participants

Full details of inclusion and exclusion criteria are outlined in Lopresti *et al.* (2014). Briefly, male and female participants aged 18 to 65 years were eligible to participate if they met the

DSM-IV criteria for current major depressive disorder and had an Inventory of Depressive Symptomatology self-rated version (IDS-SR$_{30}$) score ≥ 14. The diagnosis of major depression was made by the first author, an experienced clinical psychologist, using The Mini International Neuropsychiatric Interview 6.0 (MINI 6.0) (Sheehan et al., 1998). Participants with a psychotic disorder, bipolar disorder, comorbid obsessive-compulsive disorder, posttraumatic stress disorder, eating disorder, chronic fatigue syndrome, fibromyalgia, or any substance abuse or dependence disorder were excluded, as were participants assessed as high risk of suicide. Volunteers were also excluded if they suffered from medical illnesses including diabetes, autoimmune diseases, cardiovascular disease, hypertension, chronic fatigue syndrome, or asthma.

Interventions

Placebo (cellulose) and curcumin capsules were supplied by Arjuna Natural Extracts Ltd. Kochi, Kerala, India, and were identical in appearance. Curcumin was provided in a 500 mg capsule (BCM-95®) containing total curcuminoids 88% (curcumin, bisdemethoxycurcumin, demethoxycurcumin) and volatile oils 7% from rhizomes of *Curcuma longa* Linn. Participants were directed to take one capsule, twice daily with or without food for 8 weeks. Curcumin was administered in a dose of 1000 mg/day.

Outcomes

Depression questionnaire

Evaluation of depression and anxiety-related symptoms occurred through the administration of several self-report questionnaires as detailed in Lopresti *et al.* (2014). The Inventory of Depressive Symptomatology self-rated version (IDS-SR$_{30}$) was used as the primary assessment of depressive symptoms. Baseline and delta change in total IDS-SR$_{30}$ score was used to examine the relationship between evaluated biomarkers and depressive

symptoms. The IDS-SR$_{30}$ contains 30 items measuring depressive symptoms based on the DSM-IV criteria for major depressive episode (A. J. Rush, Gullion, Basco, Jarrett, & Trivedi, 1996). The IDS-SR$_{30}$ has acceptable psychometric properties in depressed outpatients and correlates highly with common depression inventories such as the HRSD$_{17}$, BDI, and MADRS (A.J. Rush, Carmody, & Reimitz, 2000; A. J. Rush, et al., 1996).

Laboratory assessments

Blood, urine and salivary specimens were collected from participants at baseline and endpoint (8 weeks). Participants were requested to collect blood and urine samples on the same day and salivary samples on the same day or within a day of their blood and urine collections. All collections occurred in the morning after an overnight fast. The biomarkers are described in Table 1.

Urinary collections: Participants were asked to moderately restrict fluid intake the day before testing. Participants collected overnight urine along with their first morning urine in a collection container. Samples were refrigerated until collection by researchers later that day.

Blood collections: Participants were instructed to visit a commercial local pathology centre to provide venous blood samples. They were requested to provide the blood sample after an overnight fast and before 10 am. 10mls of venous blood was drawn into lithium-heparin tubes and was centrifuged at 3000 rpm for 10 min to obtain plasma. Plasma samples were then stored at −80^{o}C for later analysis.

Salivary collections: Participants were instructed to dribble saliva in provided collection tubes within 10 minutes of awakening and 30 minutes later. Both salivary collections occurred before brushing the teeth and consumption of food or caffeinated beverages. Samples were refrigerated until collected by researchers later that day.

Urinary testing protocol: All urine samples were received on dry ice (-78°C) and stored at -80°C until testing. The samples were allowed to thaw to reach room temperature. Tbx-B2 was tested with an ELISA kit from R&D systems (cat. number KGE011), designed on the inhibition principle. LTB4 was tested with ELISA test kit from R&D systems (cat. number KGE006B). Midkine was tested with an ELISA kit from Cellmid (cat. number MKELISA), designed on the sandwich principle. Cortisol was tested with an ELISA kit from R&D systems (cat. number KGE008), designed on the inhibition principle. SUB-P was tested with an ELISA kit from R&D systems (cat. number HGE007), designed on the inhibition principle. HEVM was tested with a test from Ray Bio (cat. Number ELH-HVEM-001), designed on the sandwich principle. Aldosterone was tested with a test from LDN Germany (cat. Number MS E5200), designed on the inhibition principle. Preparation of the reagents and the testing was completed according to the procedure as described in the respective instructions for use available with all kits. The calculation of the concentrations were completed by linear interpolation uniformly for all tests (Wild, 2005). All urinary biomarkers were adjusted for creatinine concentrations.

Salivary testing protocol: Following transportation to the laboratory, saliva samples were stored at 2-8^{o}C for up to 24 hours. Untreated saliva was used directly after centrifugation. Salivary cortisol was assayed on the Roche Cobas e® analyser (manufacturer details) using a competitive polyclonal antibody immunoassay that employs a magnetic separation step followed by electrochemiluminescence quantification. 20 μL of sample was used and the assay had a measurement range of 0.5 to 1750 nmol/L (0.018-63.4 μg/dL). Results were determined via a 2-point calibration curve and a predefined master curve. The cortisol assay has a functional sensitivity of < 8.5 nmol/L (< 0.308 μg/dL) (defined as the lowest concentration reproducibly measured with precision coefficient of variation < 10%). The intra-assay coefficient of variation was < 3.6%.

Blood testing protocol: All plasma samples were received on dry ice (-78°C) and stored at -80°C until testing. The samples were thawed and allowed to reach room temperature, centrifuged 7000xg for 5 minutes to spin down and remove any clotted fibrin particles formed. Tbx-B2 was tested with an ELISA kit from R&D systems (Cat. number KGE01) based on the inhibition principle. LTB4 was tested with an ELISA kit from R&D systems (cat. number KGE006B) based on the sandwich principle. Human leptin was tested with ELISA kit from Ray Bio (cat. number SKGE006B) based on the sandwich principle. Calprotectin was tested with an ELISA kit from Hycult Biotech (cat. number HK325-02) based on the sandwich principle. Midkine was tested with an ELISA kit from Cellmid (Cat. number MKELISA) based on the sandwich principle. ET-1 was tested with an ELISA kit from R&D systems (cat. number DET100) based on the sandwich principle. Cortisol was tested with an ELISA kit from R&D systems (cat. number KGE008), designed on the inhibition principle. EGF was tested with an ELISA kit from Ray Bio (cat. number ELH-EGF-00)1 based on the sandwich principle. Human TNF-R2 was tested with an ELISA kit from Ray Bio (cat. number ELH-STNFRII-001) based on the sandwich principle. SUB-P was tested with an ELISA kit from R&D systems (cat. number HGE007), based on the inhibition principle. Preparation of the reagents and the testing were completed according to the procedures as described in the respective instructions for use available with all kits. The calculation of the concentrations was completed by linear interpolation uniformly for all tests (Wild, 2005).

Table 1: Definition of measured urinary and plasma biomarkers.

Plasma only	
Endothelin-1 (ET-1)	Protein that constricts blood vessels and raises blood pressure. In the nervous system, ET-1 plays an important role in blood pressure regulation, blood-brain barrier permeability, respiratory control and renal sympathetic neuronal activity.
Calprotectin (Cal)	Released from activated leukocytes leading to increased concentrations during bacterial infections or inflammation in relevant organs.
Leptin	Adipokine that plays a key role in regulating energy intake and expenditure, including appetite and hunger, metabolism, and behaviour.
Tumor necrosis factor receptor 2 (TNF-R2)	Binding of tumour necrosis factor (TNF) to TNFR2 results in activation and recruitment of intracellular adaptor proteins that induce signal transduction, promoting cell proliferation and survival.
Epidermal growth factor (EGF)	Growth factor that stimulates cell growth, proliferation, and differentiation. Concentrations are high in the CNS, controlling proliferation and differentiation of nervous tissue during neurogenesis.
Urine only	
Cyclic adenosine monophosphate (cAMP)	Second messenger that affects transmembrane transport, cell growth and morphology, cellular adhesion, and cytoskeletal organisation.
Herpes virus entry mediator (HVEM)	Plays a critical role in the regulation of inflammation and also serves as one of the entry receptors of herpes simplex virus.
Aldosterone	Steroid hormone that plays a central role in the regulation of blood pressure. When dysregulated, aldosterone contributes to the development and progression of cardiovascular and renal disease by promoting sodium and water retention, and lowering plasma potassium concentrations.
Urine and plasma	
Cortisol (also collected in saliva)	Hormone associated with several important processes in the body including the stress response, inflammatory and immune processes, blood sugar regulation and fat, protein, and carbohydrate metabolism.
Substance P (SUB-P)	Neuropeptide expressed predominantly in the basal forebrain, amygdala, hippocampus and diencephalon associated with nociception, respiration, cardiovascular and thermo regulation, gut motility, emetic response, and stress-related behaviour.
Leukotriene B4 (LTB4)	Lipid inflammatory mediator, generated in leukocytes from membrane arachidonic acid.
Thromboxane B2 (Tbx-B2)	An inactive metabolite of thromboxane A2 (Tbx-A2), an unstable arachidonic acid metabolite produced by activated platelets that elicits diverse physiological and pathophysiological actions, including platelet aggregation and smooth muscle contraction. In the brain, Tbx-A2 also contributes to peripheral adrenal catecholamine secretion.
Midkine	Strongly induced during oncogenesis, inflammation and repair. Promotes cell survival and cell migration, and is deeply involved in cancer progression, the onset of inflammatory diseases and the preservation and repair of injured tissues.

Statistical analysis

Effect of curcumin on evaluated biomarkers

Since the majority of the biomarkers checked by the inspection of Q-Q plots were not normally distributed and contained several outliers, logarithmic or reciprocal transformations were completed on all biomarker data. This significantly improved linearity. Therefore, repeated measures ANOVA were conducted to assess for changes in biomarker levels both within (time effects) and between groups (time x treatment). An analysis of covariance (ANCOVA) was used if differences in baseline biomarkers across groups were identified. Independent samples t-tests were used to compare baseline biomarker levels across the treatment groups. All analyses were based on complete case analyses.

Relationship between biomarkers, depression and treatment outcome

Due to the small sample sizes (approximately 20 in each condition for biomarker data), exploratory correlational analyses were conducted rather than multiple regression analysis. Correlations between delta change in IDS-SR_{30} (change from baseline to week 8) with baseline and delta change in plasma biomarkers were calculated. Correlations were examined separately for the two treatment groups. As data was not normalised and included outliers, Spearman's rho was used for correlational analyses. Where significant predictors were identified, further analyses were conducted to examine the influence of the biomarker on treatment outcome.

Significance values for statistical testing

As analyses were considered exploratory, with the goal of providing directions for future research, adjustments to significance values for multiple comparisons were not made. While it is acknowledged that this increases the risk of type I error, such analyses are considered preliminary, requiring further confirmation in more highly powered studies. For all tests, the

criterion of statistical significance was P < 0.05 (two-tailed). Since correlation coefficient values between 0.0 and 0.3 are considered weak, only correlations above 0.4 were considered clinically meaningful. All data were analysed using SPSS (version 21; IBM, Armonk, NY).

Study Population

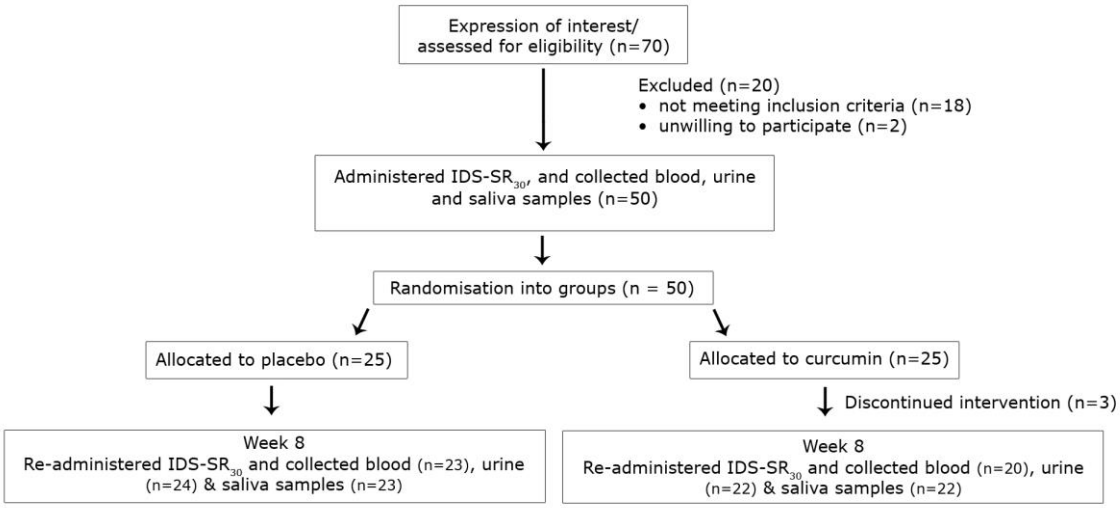

Figure 1. Systematic illustration of study design

Baseline questionnaire and demographic information

Eighty people were screened for participation in the study and 50 people met inclusion/exclusion criteria. Twenty-five people were randomised into the placebo group and 25 into the treatment (curcumin) group. Forty-seven participants completed up to week 8. There were 3 drop-outs, all from the curcumin group. As detailed in Table 2, there were no significant differences between the two groups in IDS-SR30 scores or demographic variables, except for distribution of medical illnesses, with a greater number reporting medical illnesses in the placebo (n=14) than the curcumin (n=6) group (X^2 (1) = 5.33, $p \leq .05$).

Table 2: Demographic characteristics of curcumin and placebo participants.			
	Placebo n=25	Curcumin n=25	p-value
Age (years) mean (S.D.)	48.44 (12.26)	43.00 (12.05)	0.12†
BMI (kg/m²) mean (S.D.)	27.01 (4.90)	25.98 (5.56)	0.50†
IDS-SR$_{30}$ Total Score	33.36 (12.05)	31.24 (9.10)	0.49†
Sex *n*			
Female	18	17	1.00#
Male	7	8	
Marital Status *n*			
Single	7	10	
Married	11	9	
De facto	4	4	.379#
Divorced	1	2	
Widowed	2	0	
Educational Status *n*			
Secondary	5	9	
Tertiary	16	14	.284#
Post-graduate	4	2	
General Health *n*			
Great	8	5	
Average	17	18	.257#
Poor	0	2	
Medical Illness *n*			
Yes	14	6	.021#
No	11	19	
Antidepressant Medication *n*			
Yes	9	11	.387#
No	16	14	
Exercise Frequency *n*			
Never/Rarely	6	4	
1-2 times week	8	9	.650#
3-5 times week	10	12	
6+ times week	1	0	
Injuries causing regular pain *n*			
Yes	11	9	.387#
No	14	16	

†Independent samples T-test; #Chi-square Test

Details of biomarker collections

Plasma biomarkers: 50 baseline plasma samples (25 from each condition) were collected for biomarker assessment. At baseline, EGF levels were higher in the curcumin than placebo

group, but all other biomarkers were similar in the two treatment groups. Post-plasma collections were obtained from 43 participants (curcumin, n=20; placebo, n=23).

Urinary biomarkers: 50 baseline urinary samples (25 from each condition) were collected for biomarker assessment. At baseline, urinary biomarker levels were similar in the placebo and curcumin groups. Post-urinary collections were obtained from 46 participants (curcumin, n=22; placebo, n=24).

Salivary cortisol: 50 baseline salivary samples (25 from each condition) were collected for cortisol assessment. Cortisol could not be measured in two samples (one from each condition) due to insufficient saliva collection, leaving 24 pre-salivary cortisol measurements for each condition. Baseline cortisol levels were similar in the placebo and curcumin groups. Post-salivary collections were obtained from 45 participants (curcumin, n=22; placebo, n=23).

An examination of cortisol collection times revealed no differences in average time of awakening collection pre- and post-treatment (baseline mean awakening collection time = 7.17am; week 8 mean awakening collection time = 7.14am). Average time of collection of 30-minute salivary samples also remained similar over time (baseline 30-min collection = 36 min after awakening; week 8, 30-min collection = 36 min after awakening). At baseline, 7 participants collected 30 min samples greater than 40 minutes after awakening, and at week 8, this occurred for 4 participants. As exclusion of the samples did not influence statistical outcomes and cortisol measures were not significantly different from other collections, all data were used in the analyses below.

Results

Outcome Measures

Effect of treatment condition on biomarkers

Urinary biomarkers: In the curcumin group, treatment was associated with significant increases in Tbx-B2 ($F_{1,19} = 8.21$, $p = .010$), SUB-P ($F_{1,19} = 5.59$, $p = .029$) and a similar trend for LTB4 ($F_{1,18} = 3.42$, $p = .081$). In the placebo group, there was a trend of reduced LTB4 levels ($F_{1,18} = 4.29$, $p = .052$) over time. Group x time interactions were significant for LTB4 ($F_{1,38} = 7.59$, $p = .009$), SUB-P ($F_{1,42} = 4.38$, $p = .042$) and a non-significant trend for Tbx-B2 ($F_{1,42} = 3.13$, $p = .084$) (Table 3).

Table 3: Change in biomarkers over time.

	Treatment	Baseline		Week 8		Treatment x time effect (p-value)
		Plasma Biomarkers				
LTB4	Placebo (n=23)	27.70	(66.76)	35.60	(51.84)	.511
	Curcumin (n=20)	34.90	(21.53)	27.85	(25.90)	
ET-1	Placebo (n=23)	1.43	(0.52)	1.46	(0.45)	.920
	Curcumin (n=19)	1.39	(0.25)	1.43	(0.37)	
Tbx-B2	Placebo (n=23)	3.02	(6.45)	2.86	(5.12)	.412
	Curcumin (n=20)	2.37	(7.66)	2.63	(7.30)	
Calprotectin	Placebo (n=23)	321.60	(180.30)	390.00	(226.40)	.945
	Curcumin (n=20)	330.90	(152.52)	393.30	(393.30)	
Leptin	Placebo (n=23)	919.00	(1044.14)	832.00	(856.75)	.269
	Curcumin (n=20)	494.50	(1201.54)	535.50	(1484.62)	
Midkine	Placebo (n=23)	620.00	(1235.93)	758.00	(1114.39)	.561
	Curcumin (n=23)	636.00	(1028.53)	575.00	(1156.54)	
TNF-R2	Placebo (n=23)	1760.00	(682.23)	1665.00	(787.19)	.312
	Curcumin (n=20)	1787.50	(425.23)	1690.00	(400.20)	
EGF	Placebo (n=23)	14.85	(11.95)	28.50**	(26.78)	.012
	Curcumin (n=20)	25.15	(22.98)	21.65	(17.10)	
SUB-P	Placebo (n=22)	396.00	(207.49)	337.00	(190.94)	.542
	Curcumin (n=19)	375.00	(449.20)	402.00	(326.60)	
Cortisol	Placebo (n=22)	25.73	(14.13)	21.21	(18.68)	.971
	Curcumin (n=19)	27.31	(9.13)	24.53	(13.58)	
		Urinary Biomarkers				
cAMP	Placebo (n=23)	558.50	(218.13)	545.00	(175.79)	.300
	Curcumin (n=20)	566.00	(206.93)	587.00	(214.83)	
LTB4	Placebo (n=21)	59.80	(60.60)	42.10	(21.71)	.009
	Curcumin (n=20)	40.80	(36.87)	48.10	(34.15)	
HVEM	Placebo (n=23)	15.77	(7.15)	14.05	(7.54)	.292
	Curcumin (n=20)	14.05	(4.55)	16.55	(4.73)	
Tbx-B2	Placebo (n=24)	0.50	(0.63)	0.75	(0.45)	.084
	Curcumin (n=21)	0.40	(0.66)	0.70*	(1.46)	
Midkine	Placebo (n=22)	23.76	(17.97)	26.14	(8.47)	.771
	Curcumin (n=19)	24.15	(24.15)	24.66	(43.93)	
SUB-P	Placebo (n=24)	9.50	(33.19)	4.43	(21.81)	.042
	Curcumin (n=21)	16.20	(32.24)	64.12*	(67.05)	
Cortisol	Placebo (n=19)	3.87	(3.42)	2.67	(2.10)	.141
	Curcumin (n=20)	3.58	(2.97)	4.20	(3.43)	
Aldosterone	Placebo (n=24)	355.00	(257.06)	251.25	(187.17)	.114
	Curcumin (n=21)	340.00	(204.48)	343.00	(147.28)	

Significant within-group time effects * (p<.05); **(p<.01)
Data are shown as median (S.D.)
Values expressed as plasma pg/mL and urine mg/creatinine

Plasma biomarkers: EGF increased after treatment in the placebo group but remained stable in the curcumin group ($F_{1,37} = 5.24$, $p = .028$). An ANCOVA was conducted to control for the effects of differing baseline EGF levels across treatment groups (baseline EGF was entered as a covariate), and the difference between groups was no longer significant ($F_{1,39} = 1.57$, $p = .218$).

There were no other significant time or group x time interaction for other measured plasma biomarkers (Table 3).

Salivary cortisol: Pre- and post-intervention levels of salivary cortisol across each treatment condition are detailed in Table 4. Cortisol levels did not change significantly over time in either treatment condition and there were no significant between-group differences.

Table 4: Change in salivary cortisol over time.

	Treatment	Baseline (nmol/L)		Week 8 (nmol/L)		Treatment x time effect (p-value)
Cortisol awake, median (SD)	Placebo (n=23)	21.50	(14.14)	22.00	(14.14)	.91
	Curcumin (n=22)	24.50	(14.14)	24.50	(21.11)	
Cortisol 30 min, median (SD)	Placebo (n=23)	22.00	(15.96)	23.00	(22.05)	.34
	Curcumin (n=22)	24.00	(10.30)	23.50	(18.04)	
Cortisol CAR, median (SD)	Placebo (n=23)	1.00	(11.77)	1.00	(23.73)	.75
	Curcumin (n=22)	-1.50	(16.14)	-2.50	(17.89)	

CAR = cortisol awakening response (absolute change between awakening and 30 min cortisol).

Relationship between biomarkers, depression and treatment outcome

Correlations between IDS-SR_{30} total score and biomarker levels (baseline levels and change in levels) are detailed in Tables 5 and 6. In placebo group, lower baseline urinary cAMP was associated with a greater reduction in the IDS score after 8 weeks of treatment (r_s = .461; p = .023). In the curcumin group, higher baseline plasma ET-1 (r_s = -.585; p = .004) and plasma leptin (r_s = -.451; p = .040) were associated with greater reductions in the IDS score after 8 weeks of treatment.

In the placebo group, decreases in IDS-SR_{30} were associated with increases in plasma cortisol (r_s = -.544; p = .009), plasma ET-1 (r_s = -.496; p = .016), and urinary HVEM (r_s = -.437; p = .037). In the curcumin group, decreases in IDS-SR_{30} were associated with decreases in plasma leptin (r_s =.515; p = .024).

Table 5: Spearman's rank-order correlations between IDS-SR30 total score and plasma biomarker levels (baseline levels and change in levels).

			LTB4	ET-1	Tbx-B2	Calprotectin	Leptin	Midkine	TNF-R2	EGF	Substance P	Cortisol
Change in IDS score and baseline biomarker level	Placebo	rs	.160	.022	-.078	.053	.030	.003	.094	-.136	.151	-.302
		p-value	.446	.916	.712	.801	.888	.987	.655	.526	.473	.142
		n	25	25	25	25	25	25	25	24	25	25
	Curcumin	rs	.307	-.585**	.049	-.059	-.451*	-.001	-.145	-.107	-.005	.115
		p-value	.176	.004	.833	.801	.040	.996	.530	.643	.984	.621
		n	21	22	21	21	21	21	21	21	21	21
Change in IDS score and change in biomarkers level	Placebo	rs	-.377	-.496*	-.373	-.404	.193	-.294	-.282	-.025	-.144	-.544**
		p-value	.076	.016	.079	.056	.378	.173	.192	.910	.522	.009
		n	23	23	23	23	23	23	23	23	22	22
	Curcumin	rs	-.215	-.154	-.300	-.111	.515*	.033	.290	.300	-.147	-.055
		p-value	.363	.528	.199	.652	.024	.890	.229	.199	.549	.829
		n	20	19	20	19	19	20	19	20	19	18

Table 6: Spearman's rank-order correlations between IDS-SR30 total score and urinary biomarker levels (baseline levels and change in levels).

			cAMP	LTB4	HVEM	Tbx-B2	Midkine	Substance P	Cortisol	Aldosterone
Change in IDS score and baseline biomarker level	Placebo	rs	.461*	.174	.355	.144	-.065	.318	.204	.085
		p-value	.023	.438	.089	.493	.769	.122	.388	.685
		n	24	22	24	25	23	25	20	25
	Curcumin	rs	-.308	-.194	-.153	-.259	.228	-.007	.194	-.053
		p-value	.174	.398	.508	.245	.333	.974	.400	.814
		n	21	21	21	22	20	22	21	22
Change in IDS score and change in biomarkers level	Placebo	rs	-.248	-.353	-.437*	-.035	-.044	-.107	-.108	-.004
		p-value	.253	.117	.037	.869	.846	.619	.660	.986
		n	23	21	23	24	22	24	19	24
	Curcumin	rs	-.223	-.052	.147	.091	-.354	-.173	-.131	-.253
		p-value	.344	.826	.536	.695	.137	.455	.582	.269
		n	20	20	20	21	19	21	20	21

As baseline plasma ET-1 and leptin in the curcumin group, and urinary cAMP in the placebo-group, were significantly associated with change in the IDS-SR30 score, further exploratory analyses were conducted. Participants with high baseline ET-1 (defined as an ET-1 level above the total sample mean of 1.47) (n=19) were selected for further analysis. Baseline demographics were similar in the curcumin and placebo groups except for significant differences in age (mean difference = 9.20, 95% CI [0.41, 17.02], $t(17) = -2.27$, $p = .037$) and medical illness (X^2 (1) = 10.05, p- = .002). Hence, these variables were included as covariates in

a repeated measures ANOVA. In participants with a high baseline ET-1, curcumin was more effective than placebo in reducing IDS-SR_{30} as evidenced by a significant group x time interaction ($F_{2,30}$ = 3.82, p = .033; Cohen's d = 1.26) (Figure 2). No similar significant patterns were observed with baseline leptin or cAMP levels.

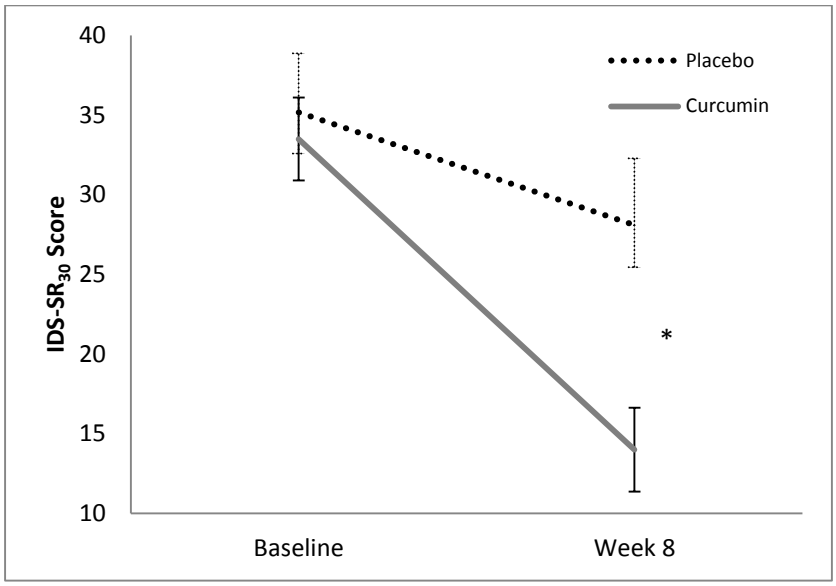

Figure 2. Change in IDS-SR_{30} total score over time *(± std. error)* across curcumin and placebo groups in participants with a high ET-1 level at baseline (> 1.47). * indicates significant group x time interaction ($p < 0.05$).

Discussion

Curcumin and its effect on biomarkers

Compared to placebo, eight weeks of curcumin supplementation was associated with significant changes in several measured biomarkers. Urinary levels of Tbx-B2, SUB-P, and LTB4 (non-significant trend) increased in curcumin-treated individuals whereas in placebo-treated individuals plasma EGF decreased significantly and LTB4also declined (non-significant trend).

SUB-P: SUB-P is a neuropeptide expressed predominantly in the basal forebrain, amygdala, hippocampus and diencephalon. It is associated with nociception, respiration, cardiovascular and thermo-regulation, gut motility, emetic response, and stress-related behaviour (Holmes, Heilig, Rupniak, Steckler, & Griebel, 2003). A role of SUB-P in depression is supported by evidence confirming that SUB-P and its preferred receptor neurokinin-1 (NK1) are activated by stressors which, in turn, stimulate HPA axis activity (Ebner & Singewald, 2006). They are also associated with the modulation of noradrenaline and serotonin (Blier et al., 2004). Although evidence is mixed, anxiolytic and antidepressant properties of NK1 antagonists have been identified both in animal and human studies (Holmes, et al., 2003). Elevated concentrations of SUB-P in the cerebrospinal fluid (CSF) and serum of depressed patients have also been reported, and SUB-P levels decrease in some responders following antidepressant treatment (Alldredge, 2010).

Investigations into the effects of curcumin on SUB-P are limited. In a recent randomised double-blind placebo-controlled trial, curcuminoids as an adjunct to chemotherapy significantly lowered serum SUB-P in patients with cancer (Panahi, Saadat, Beiraghdar, & Sahebkar, 2014). Similar effects were observed following curcumin administration in patients treated for pruritic symptoms induced by sulphur mustard (Panahi et al., 2012). In the present study, curcumin administration was not associated with changes in plasma SUB-P, but was associated with increased urinary concentrations. Given previous findings of increased plasma concentrations in major depression, this observation is contrary to what one might expect from an antidepressant agent. However, urinary SUB-P was not measured in any previous study. Potentially, urinary increases in SUB-P reflect increased excretion, followed by reduced plasma concentrations over the longer term. In addition, a urine collection comprising overnight and first morning voids may be more sensitive to changes in biomarkers

than a single point, fasting plasma collection. Further investigation is necessary to help elucidate the relevance of this finding and how it relates to depression treatment.

LTB4: LTB4 is a lipid inflammatory mediator generated in leukocytes from membrane arachidonic acid by the sequential actions of cytosolic phospholipase A2, 5-lipoxygenase (5-LOX) and leukotriene A4 hydrolase. Several inflammatory diseases, including asthma, chronic obstructive pulmonary disease, arthritis and cardiovascular disease, are associated with elevated levels of LTB4 (Singh, Tandon, Dastidar, & Ray, 2013). Although depression is associated with increased inflammation, surprisingly little research has specifically investigated LTB4 in major depression. In the only identified study, 12 single nucleotide polymorphisms (SNPs) in the leukotriene A4 hydrolase gene were not associated with depressive symptoms (Zhao et al., 2009). In an animal model of depression, inhibition of 5-LOX, an enzyme involved in leukotriene synthesis, produced antidepressant-like effects (Dzitoyeva et al., 2008). In contrast to this finding, there are reports of increased suicide-related adverse events associated with the use of leukotriene receptor antagonists (Schumock et al., 2011).

Curcumin inhibits the incorporation of LTB4 into membrane lipids (Joe & Lokesh, 1997) and inhibits LTB4 formation in rat peritoneal polymorphonuclear neutrophils (Ammon, Anazodo, Safayhi, Dhawan, & Srimal, 1992). Curcumin also regulates 5-LOX activity which is associated with LTB4 production (Shehzad, Rehman, & Lee, 2013). In contrast to these inhibitory effects, curcumin administration was associated with increased urinary LTB4 compared to a placebo in the present study. The significance of this finding is unclear as change in LTB4 was not associated with change in depressive symptoms. As hypothesised with SUB-P, urinary increases may be a more immediate or sensitive marker of change than plasma collections. Longer follow-up periods will be necessary to determine if this pattern occurs.

Tbx-B2: Tbx-B2 is an inactive metabolite of thromboxane A2 (Tbx-A2). Tbx-A2, an unstable arachidonic acid metabolite, is produced by activated platelets that elicit diverse physiological and pathophysiological actions, including platelet aggregation and smooth muscle contraction (Sellers & Stallone, 2008). In the brain, Tbx-A2 also contributes to peripheral adrenal catecholamine secretion (Okada, Murakami, & Yokotani, 2003). Elevated levels of Tbx-B2 have been found in patients with major depression , with positive correlations between cortisol and Tbx-B2 (Piccirillo et al., 1994). Treatment with sertraline in individuals with cardiac illness and comorbid depression decreased Tbx-B2 significantly after 16 weeks (Serebruany et al., 2003).

Curcumin inhibits Tbx-B2 production in human platelets (Shah et al., 1999). In the present study, urinary levels trended upward after curcumin treatment but decreased following placebo intervention. This finding is contrary to what one might expect from an antidepressant agent, given findings of elevated blood levels in depressed patients and reductions associated with antidepressant therapies. However, Tbx-B2 concentrations have not previously been measured in urinary samples, which may account for this discrepant finding. As hypothesised with SUB-P and Tbx-B2, urinary increases may be transient, reflecting increased excretion.

EGF: EGF is a polypeptide that stimulates the proliferation of different cell types, especially fibroblasts and epithelial cells. In the central nervous system, EGF mRNA has been detected in several regions, including the brainstem, cerebellum, cerebral cortex, hippocampus, olfactory bulb, and striatum (Plata-Salaman, 1991). EGF concentrations are high in the CNS and play a critical role in controlling proliferation and differentiation of nervous tissue during neurogenesis (Xian & Zhou, 1999). EGF is also important in promoting wound healing and is expressed at sites of injury, inhibiting the activity of nitric oxide synthase and

dampening inflammation (Heck, Laskin, Gardner, & Laskin, 1992). In animal models, EGF deficiency results in several neurological, gastrointestinal, dermal, and pulmonary abnormalities (Miettinen et al., 1995). Acute and chronic pathological processes, particularly cancers, can stimulate the production and release of EGF in various cell systems (Bodnar, 2013). EGF levels are also elevated during periods of prolonged stress (Asberg et al., 2009). Investigations into EGF concentrations in major depression are limited and in the only identified study, plasma EGF levels were significantly lower in depressed patients than in a control group (Tian et al., 2012).

Studies on the effects of curcumin on the EGF system have largely investigated its role as a cancer treatment, where it down-regulates EGF receptor function and EGF expression (Shishodia, 2013). In the current study, curcumin did not change EGF concentrations, whereas placebo treatment was associated with increases in EGF levels. The causes for this are unknown and may simply be a reflection of differences in baseline concentrations of EGF across the two treatment groups (i.e., baseline EGF levels were higher in the curcumin group compared to the placebo group). However, it remains possible that curcumin buffered nonspecific increases in EGF concentrations over the course of treatment. The significance of this finding and its relevance to depression treatment requires further examination in more highly powered studies.

Baseline biomarkers and their relationship to change in depression following curcumin treatment

In curcumin-treated individuals, higher baseline plasma levels of ET-1 and leptin were associated with greater improvements in depressive symptoms. Further support for the importance of ET-1 in curcumin treatment was obtained in additional exploratory analyses. When individuals with high baseline ET-1 levels were examined (i.e. greater than the total sample mean of 1.47 pg/ml), curcumin had significantly greater efficacy in lowering IDS-SR_{30}

scores (indicated by a significant group x time interaction). A large Cohen's d effect size of 1.26 was observed in curcumin-treated individuals compared to placebo.

Given limitations associated with the small samples size in this study and the risk of type I error due to multiple correlational analyses, these findings should be considered preliminary and certainly require confirmation from studies with larger sample sizes. However, if this relationship can be replicated, treatment outcome might be enhanced by improved treatment-matching. Potentially, depressed individuals with higher baseline ET-1 (and possibly leptin) have a greater likelihood of successful treatment with curcumin.

ET-1: ET-1, a peptide with potent vasoactive effects, is widely expressed in brain cells. Altered expression of ET-1 in reactive astrocytes has been observed in many pathological conditions including infarcts, Alzheimer's disease and inflammatory diseases of the brain (Schinelli, 2006). In the nervous system, ET-1 plays an important role in blood pressure regulation, blood-brain barrier permeability, respiratory control and renal sympathetic neuronal activity (Khimji & Rockey, 2010). There is also evidence that ET-1 and its associated receptors interact with dopamine release (van den Buuse & Webber, 2000). ET-1 also influences free radical production (Piechota, Polanczyk, & Goraca, 2010), HPA activity (Kiefer, Kellner, Jahn, & Wiedemann, 2000), and cytokine production (Giordano, Papakostas, Pecetti, & Nuti, 2011).

From research on the endothelin system in major depression, an impaired endothelial function in depressed individuals has been demonstrated (Wagner et al., 2012), and severity of depressive symptoms predicted ET-1 elevations in patients with coronary artery disease (Burg, Martens, Collins, & Soufer, 2011). In the CSF, ET-1 concentrations were also reduced by approximately 50% in patients with major depression (Hoffman et al., 1989). Bosentan, a mixed endothelin receptor antagonist, also demonstrated antidepressant activity in mice (Pinho-Ribeiro et al., 2014).

Investigations into the effects of curcumin on the endothelin system are limited although curcumin inhibited ET-1 induced mitogenic and proliferative signalling events in vascular smooth muscle cells (Kapakos, Youreva, & Srivastava, 2012), and in diabetes-induced rats curcumin increased ET-1 concentrations in microvascular endothelial cells (Farhangkhoee, Khan, Chen, & Chakrabarti, 2006). In the present study curcumin did not alter ET-1 concentrations, suggesting that the enhanced antidepressant efficacy of curcumin in people with higher concentrations of ET-1 were not due to its ET-1-lowering effects. The effects of curcumin may therefore be related to influences on endothelin receptor sensitivity or on inflammatory, HPA axis or oxidative stress processes which have been shown to be influenced by ET-1 concentrations.

Relationship between change in biomarkers and change in depression following curcumin treatment

In curcumin-treated individuals, reductions in leptin were associated with reductions in depressive symptoms. This association was not observed in placebo-treated individuals, indicating that it may be specifically related to the effects of curcumin. However, in placebo-treated individuals, increases in urinary concentrations of ET-1, cortisol, and plasma HVEM were associated with reductions in depressive symptoms.

Leptin, a peptide hormone secreted from adipocytes, plays a significant role in suppressing food intake and stimulating energy expenditure. Leptin concentrations are elevated in obesity, although its appetite-suppressing effects in obese individuals are thought to be compromised (Zhou & Rui, 2013). Leptin resistance may occur at several levels due to impaired transport of leptin across the blood brain barrier, a reduction in the function of leptin receptors, and damage to leptin signal transduction (Munzberg & Myers, 2005). Variability in leptin concentrations is commonly observed in major depression, though there are inconsistences in the direction of change. In the majority of animal-based studies lower levels

of leptin are associated with depressive behaviours. Human-based studies are inconsistent, with reports of increased and decreased leptin concentrations in depressed individuals (Lu, 2007; Zupancic & Mahajan, 2011). It is believed that a state of leptin resistance, and factors such as age, sex and BMI, are major reasons for this inconsistent data (Lu, 2007). A role of leptin in depression is also supported by studies showing antidepressant properties of leptin and its ability to influence monoamine activity, HPA regulation, neurotrophic actions, and immune responses (Lu, 2007).

Investigations into the effect of curcumin on leptin levels and signalling have confirmed its influential effects. In animal and *in vitro* models, curcumin lowered leptin concentrations induced by various dietary and inflammatory stressors (Lee et al., 2013). In a 6-month randomised, double-blind, placebo controlled trial on adults with type 2 diabetes, curcumin significantly decreased leptin levels (Chuengsamarn, Rattanamongkolgul, Phonrat, Tungtrongchitr, & Jirawatnotai, 2014).

In the present study, the significance of leptin in major depression was further confirmed. At baseline, higher leptin levels were associated with greater antidepressant benefits from curcumin. In curcumin-treated individuals, reductions in leptin levels were also associated with reductions in depressive symptoms. While curcumin did not significantly lower leptin concentrations compared with placebo, benefits may have been derived from its effect on leptin receptor sensitivity or other metabolic factors associated with leptin. Alternatively, the lack of statistical power due to low sample sizes and lack of control for confounders (e.g., gender and BMI) may have hidden real changes in leptin induced by curcumin. Greater time intervals may also be required for curcumin to have an effect on leptin concentrations in plasma.

Limitations and Directions for Future Research

The relatively small samples size and the large number of statistical analyses used in this study limits the reliability and statistical power associated with the findings. For evaluation of biomarker changes over time, samples of less than 40 were often used and numbers were even lower when examining the antidepressant effects of curcumin on people with high ET-1. The likelihood of type 1 error is also increased due to multiple statistical testing. The results from this study therefore require replication with larger sample sizes using greater controls for type 1 error.

Given problems associated with testing and biomarker stability, greater control around sample collection, storage, testing, and comparisons with non-depressed, matched samples will also be important. In the current study, participants were requested to collect samples in their home and to visit a local pathology centre for blood collection. Although convenient for participants, this may have increased variation in the time of collection and storage conditions of samples.

Differences in findings across urine and plasma samples also require further clarification. In the present study, biomarker correlations across the plasma and urine samples were low and their response to curcumin supplementation was variable. In particular, greater understanding of urinary measurements are required to help decipher the most reliable and responsive sampling method for biomarker evaluation.

As several markers of oxidative stress and activated immune-inflammatory pathways are associated with depression, testing for additional markers such as malondialdehyde, 8-oxo-2'-deoxyguanosine, CRP, tryptophan catabolites along the kynurenine pathway, and selected cytokines would also be helpful (Adrian L. Lopresti, et al., 2014). Evaluation of biomarkers at more frequent intervals and comparisons with a healthy control group may also improve understanding about the mechanisms associated with the antidepressant actions of curcumin.

In this study the effect of curcumin on individual biomarkers was examined. However, given the multiple potential actions of curcumin, and the several mechanisms associated with major depression, it is unlikely that using a single biomarker in isolation will fully explain the antidepressant effects of curcumin. Improved sensitivity and specificity around diagnosis, treatment matching, and evaluation of treatment progress is only likely when multiple markers are collectively examined. This requires further research using larger sample sizes and the use of pattern analysis to identify relevant biomarker algorithms.

While this 8-week study now represents the longest trial investigating the antidepressant effects of curcumin, greater treatment periods may be beneficial. Longer administration of curcumin may be necessary for curcumin to have effects on evaluated biomarkers. For example, in one study on people with osteoarthritis, reductions in IL-6, ESR and IL-1β continued for 8 months after treatment (Belcaro et al., 2010). Investigations to determine the optimal curcumin dosage and frequency of administration will also be useful.

Finally, greater control for potential covariates such as medication use, medical illnesses and BMI will increase the strength of future findings, as will the use of clinician-rated instruments and the improved monitoring of curcumin intake, possibly through blood analysis.

Conclusions

In this randomised, double-blind, placebo controlled study several important preliminary findings were identified:

1. Compared to a placebo, 8 weeks of curcumin supplementation was associated with elevations in urinary levels of LTB4, Tbx-2 and SUB-P. In placebo-treated individuals there were increases in plasma levels of EGF, while no changes were observed following curcumin treatment. Determining reasons for these increases in urinary

biomarkers are difficult as they were mostly opposite to what might be hypothesised from both curcumin and antidepressant treatment. Investigations with larger samples and comparisons with non-depressed, matched populations will enhance understanding of these findings. One possible explanation is that baseline levels were low in the depressed sample and then normalised following curcumin treatment. Alternatively, elevated urinary levels may be a reflection of increased urinary excretion with a stabilisation or even reduction in urine and/or plasma over the longer term. Biomarkers measured through urinary samples as opposed to blood samples may also account for these discrepant results. The collective examination of biomarkers rather than in isolation may also increase clarification about the mechanisms associated with curcumin supplementation.

2. In depressed individuals, higher baseline levels of plasma ET-1 were associated with an enhanced antidepressant benefit from curcumin supplementation. On the whole, people with high baseline ET-1 levels (above 1.47 pg/ml) experienced significant antidepressant benefits from curcumin. Interpreting this finding is difficult as curcumin supplementation was not associated with changes in ET-1 levels. It is speculated that curcumin enhanced endothelin receptor sensitivity or some other mechanism associated with ET-1 production which, in turn, had antidepressant effects.
3. In depressed individuals, higher baseline levels of plasma leptin were associated with an enhanced antidepressant benefit from curcumin supplementation. Moreover, a reduction in plasma leptin levels in curcumin-treated, depressed patients was associated with improvements in depressive symptoms. This suggests that the antidepressant benefits from curcumin are at least partly derived from is effect on leptin and possibly leptin resistance.

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Chapter 7:
Conclusions & Recommendations

As has been detailed previously, the aims of this thesis are outlined below:

Aim 1: Review dysregulated biological pathways associated with major depression and examine the influence of lifestyle-based factors; and psychological and pharmacological interventions on these pathways.

Aim 2: Review studies investigating the influence of curcumin on depressogenic biological pathways and, through a randomised, double-blind, placebo-controlled study, investigate its antidepressant efficacy in people with major depressive disorder.

Aim 3: Review and investigate the potential of peripheral biomarkers to evaluate treatment success, identify antidepressant mechanisms of change and predict treatment response. This was subsequently examined in a clinical study evaluating the efficacy of curcumin for the treatment of depression.

Conclusions, limitations and recommendations for future research associated with each of these aims are outlined below.

Aim 1: Dysregulated biological depressogenic pathways and important influences

In previous chapters it was demonstrated that major depression is associated with several dysregulated biological pathways which can be influenced by an array of past and current lifestyle, psychological, and biological factors. Consequently, it is hypothesised that positive lifestyle changes in these areas, along with psychological, pharmaceutical, nutraceutical and biological-based treatments, can lead to a resolution of depressive symptoms. As detailed in Figure 3, these changes have the potential to normalise biological pathways and consequently lead to improvements in depressive symptoms. Improved mood and cognitive outlook are

also likely to contribute to positive lifestyle-based changes, further normalising these biological pathways.

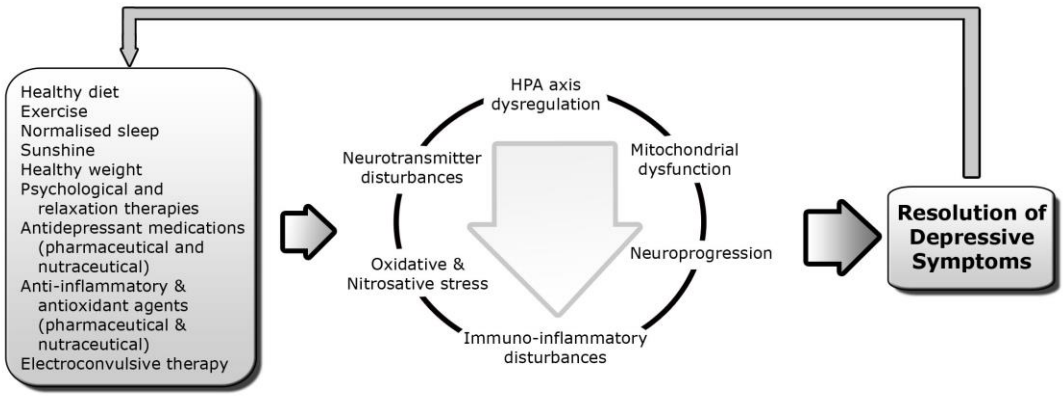

Figure 3. *Treatment options to reduce dysregulated biological pathways associated with major depression.* Several lifestyle, dietary, psychological, pharmacological and nutraceutical options (left of figure) can promote positive changes in the dysregulated biological pathways (centre of figure). Improvements in depressive symptoms may ensue, leading to further positive lifestyle, dietary and psychological changes (represented by top arrow). A feed-forward process ensues with increasing symptom resolution over time.

However, there remain several areas that require further investigation. While the reviewed lifestyle factors are commonly associated with major depression, association does not confirm causation, and greater control for confounding variables is necessary. High-quality interventional studies are also needed, particularly examining dietary treatments for major depression. Although a healthy diet is protective against depression, there is currently a lack of studies examining the efficacy of dietary interventions on depressive symptoms in people with major depressive disorder. The same also applies with investigations into the efficacy of weight-loss interventions for people with depression. In addition, while it has been hypothesised that positive lifestyle changes normalise dysregulated biological pathways and lead to consequent improvements in depressive symptoms, this has received very little attention in the research literature. Even though positive lifestyle changes, psychological

therapies and pharmaceutical interventions are effective treatments for depression, it is currently unknown whether a normalisation in biological pathways is essential for symptomatic improvements to occur. This topic has been investigated in several pharmaceutical trials but findings are inconsistent. Finally, the efficacy of psychological therapies has traditionally been measured through clinician-administered and self-report inventories. However, the inclusion of biomarker evaluation will also help to expand understanding into the biological mechanisms of change associated with psychological therapies.

Aim 2: Curcumin for the treatment of major depression

While several nutraceuticals have demonstrated efficacy for the treatment of mild-to-moderate major depressive disorder, clinical studies on the antidepressant effects of curcumin are scarce. Given the influence of curcumin on several antidepressant biological mechanisms, it was hypothesised that curcumin would be an effective treatment for major depressive disorder. This was evaluated in the first randomised, double-blind, placebo controlled study on people with major depression. Overall, findings from this study provide initial support for the antidepressant effects of curcumin in people with major depressive disorder. As detailed in Lopresti *et al.* (2014a) curcumin was significantly more effective than a placebo for the treatment of major depression, with greater improvements occurring from weeks 4 to 8. Limitations associated with this study and recommendations for future research have already been covered in Lopresti *et al.* (2014a) and comprise the following:

- Problems associated with small sample sizes.
- The examination of only a single dosage (1000 mg/day), duration (8-weeks) and frequency (twice daily) of curcumin supplementation.
- The sole use of self-report inventories to measure symptomatic treatment response.

- Limited evaluation of potential confounding variables e.g., antidepressant medication, psychological therapy, acute and chronic depression, age and gender.
- Investigation into the potential and suitability of curcumin as a stand-alone or adjunctive treatment for major depression.
- Further examination into the efficacy of curcumin on differing depressive subtypes. This is particularly pertinent given the preliminary finding of greater antidepressant benefits associated with atypical depression.

Although the primary goal of this thesis was to investigate the antidepressant efficacy of curcumin, there remain an array of other nutraceuticals with potential antidepressant efficacy. One example includes *Crocus sativus* (saffron) which has demonstrated efficacy for the treatment of mild-to-moderate depressive disorder. A published systematic review on the use of saffron for the treatment of major depression is included in Appendix 1 (Lopresti and Drummond, 2014).

Aim 3: Peripheral biomarkers and depression: its application in a curcumin trial

The role of peripheral biomarkers for diagnostic, treatment-evaluative and treatment-matching purposes in major depression also comprised a significant component of this thesis. The following hypotheses were made:

1. The antidepressant mechanisms associated with curcumin can be evaluated through pre- and post-collections of peripheral biomarkers.
2. Curcumin will have greater antidepressant efficacy for specific subgroups of individuals with major depressive disorder. These subgroups can be identified through baseline biomarker concentrations which may facilitate patient-treatment matching and therefore increase treatment success.

Overall, both these hypotheses received preliminary support. Changes in urinary leukotriene B4, thromboxane B2 and substance P were significantly associated with changes in depressive

symptoms following curcumin treatment, and provide indications of the potential antidepressant mechanisms of curcumin. In addition, higher baseline plasma concentrations of endothelin-1 and leptin were associated with increased treatment efficacy. The relevance of these findings has been fully explored in Lopresti, *et al.* (2014c). Limitations associated with the study and recommendations for future research have also been explored in this paper. Briefly, some of the limitations included:

- No biomarker comparisons with healthy, matched populations.
- Limited frequency of biomarker measurements i.e., collections were only undertaken at baseline and end-point.
- Problems associated with multiple statistical tests and consequent increased risk for type 1 error.
- Limited control and investigation into biomarker collection, storage and testing protocols.

In addition, there remains an array of potential peripheral biomarkers that were not examined in this clinical trial, and many of them were outlined Lopresti *et al.* (2014b). Examples include biomarkers assessing immuno-inflammation such as CRP, pro-inflammatory cytokines and TRYCATs (e.g., kynurenine, kynurenic acid and quinolinic acid); and markers of oxidative and nitrosative stress such as 8-hydroxy-2-deoxyguanosine, malondialdehyde and conjugated nitric-oxide adducts. These biomarkers could not be measured in this clinical trial due to financial constraints but may provide further indications about the potential mechanisms of change associated with curcumin treatment and may facilitate improved treatment-matching.

Findings from this study have also highlighted the potential utility of biomarker testing in major depression and it is recommended that biomarkers be more consistently investigated in future clinical trials utilising lifestyle, psychological and pharmaceutical treatments. While

progress in improving treatment response rates over the past decade has been disappointing, the addition of biomarker evaluations may improve patient-treatment matching and therefore increase the likelihood of treatment success.

Summary

In sum, investigations from this thesis add to the current depression research literature through several areas. First, lifestyle effects on depressogenic biological pathways have been comprehensively reviewed and areas for future research are suggested. Second, preliminary support for the antidepressant effects of curcumin in people with major depressive disorder has been provided. Further research is required to replicate the current findings. Third, the potential of peripheral biomarkers to examine antidepressant mechanisms of change and facilitate treatment matching has been reviewed and investigated in a clinical trial using curcumin. The potential of biomarker assessments to increase treatment response rates through improved treatment matching has also been reviewed.

Major depression is a common disorder that causes significant suffering for individuals and their family. While effective treatments are available, they are far from perfect. It is hoped that with further research in the areas covered in this thesis, we can expand our understanding of this complex disorder and improve treatment efficacy.

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Saffron (*Crocus Sativus*) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action

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Abstract

BACKGROUND: Saffron, a spice derived from the flower of *Crocus sativus*, has now undergone several trials examining its antidepressant effects, and in a recent meta-analysis, was confirmed to be effective for the treatment of major depression.

OBJECTIVE: To provide an expanded systematic analysis of the completed clinical studies on saffron and depression, detailing dosages, extract sources, standardisations, safety profile and treatment duration; and, through a narrative review, examine its potential antidepressant mechanisms of action.

DESIGN: In the systematic review of clinical trials, electronic databases were searched for high-quality, randomised, double-blind studies, with placebo or antidepressant-controls. A narrative review of *in vivo* and *in vitro* studies was conducted to examine its potential antidepressant mechanisms of action.

RESULTS: In the systematic review, six studies were identified. In the placebo-comparison trials, saffron had large treatment effects and when compared to antidepressants medications, had similar antidepressant efficacy. Saffron's antidepressant effects potentially are due to its serotonergic, antioxidant, anti-inflammatory, neuro-endocrine and neuroprotective effects.

CONCLUSIONS: Research conducted so far provides initial support for the use of saffron for the treatment of mild to moderate depression. Further research is required to expand our understanding of the role and actions of saffron in major depression.

Introduction

Saffron is the dried elongated stigmas and styles of the blue-purple saffron flower (Crocus sativus, L.). At a retail price of up to USD $11,000 per kilogram it is the world's most expensive spice, reflected by the labour intensiveness associated with its production. It is estimated that it takes approximately 150,000 crocus blossoms or 450,000 hand-picked stigmas to produce just one kilogram of this unique spice (Melnyk et al., 2010, Schmidt et al., 2007).

Saffron stigmas contain four major bioactive compounds (Figure 1); crocins (family of six mono-glycosyl or di-glycosyl polyene esters), crocetin (a natural carotenoid dicarboxylic acid precursor of crocin), picrocrocin (monoterpene glycoside precursor of safranal and product of zeaxanthin degradation), and safranal. Crocins and crocetin are responsible for the colour, pricrocrocin the taste, and safranal the aroma, although collectively these compounds are responsible for the health-enhancing properties associated with saffron (Melnyk et al., 2010, Moghaddasi, 2010). In addition to these compounds, saffron contains in excess of 150 volatile and aroma-yielding compounds and many non-volatile active components, many of which are carotenoids, including zeaxanthin, lycopene, beta-carotenes and polysaccharides (Sampathu et al., 1984).

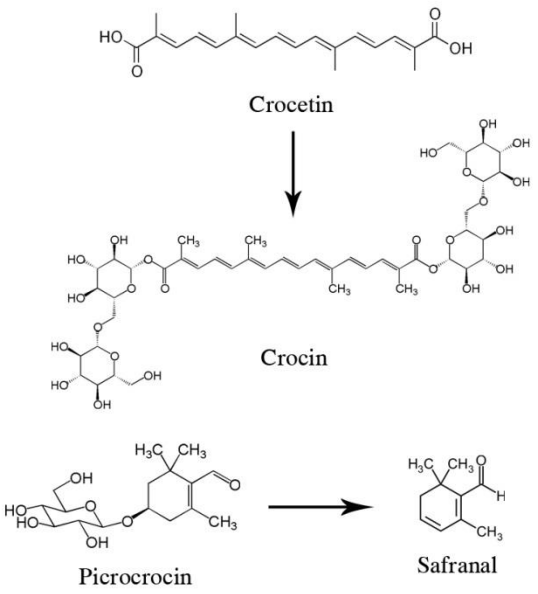

Figure 1. Chemical structures of major components in saffron

As a result of its characteristic bitter taste, pungent hay-like aroma and luminous yellow-orange colour, saffron is used in fragrances, flavourings, colouring agents and medicines (Melnyk et al., 2010). In traditional medicine, saffron has been used as an anticonvulsive, analgesic, aphrodisiac, antispasmodic and expectorant (Hosseinzadeh and Nassiri-Asl, 2013). Modern pharmacological studies have demonstrated that extracts of saffron stigmas have anticancer, anti-inflammatory, antioxidant and antiplatelet effects (Moshiri et al., 2006, Wang et al., 2010). Recent clinical trials have also suggested a potential for saffron in the treatment and prevention of Alzheimer's disease (Akhondzadeh et al., 2010a, Akhondzadeh et al., 2010b) and macular degeneration (Falsini et al., 2010, Piccardi et al., 2012). Saffron also has the potential to enhance mental health through it antidepressant properties and in a recent meta-analysis was confirmed to be effective for the treatment of depression (Hausenblas et al., 2013). The purpose of this review is to examine the potential underlying antidepressant mechanisms of action of saffron, and provide an expanded systematic analysis of the

completed clinical studies on saffron and depression, detailing dosages, extract sources, standardisations, safety profile and length of treatment.

Potential antidepressant mechanisms of action of saffron

Given the many active constituents contained in saffron it has several potential antidepressant mechanisms of action. A review of *in vitro* and *in vivo* animal or human-based studies indicate that some of the underlying mechanisms which have relevance for the treatment of depression include its antioxidant, anti-inflammatory, serotonergic, hypothalamus-pituitary-adrenal (HPA) axis-modulating and neuroprotective effects.

Antioxidant effects

Major depression is associated with elevated levels of oxidative stress and reduced antioxidant defences (Maes et al., 2011, Maes et al., 2012b, Palta et al., 2014). In a recent meta-analysis on twenty-three studies with 4980 participants, an increased oxidative stress and lowered antioxidant status among individuals with depression was confirmed (Palta et al., 2014). Depression is specifically associated with lowered antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase, and increased markers of oxidative stress such as malondialdehyde (MDA) (Lopresti et al., 2014). It is posited that increased oxidative stress in depression influences inflammatory and immune responses, disrupts neurotransmitter balance and contributes to increased neurodegeneration (Leonard and Maes, 2012).

Saffron, and its constituents, crocin, crocetin and safranal, are potent antioxidants. In animal studies, safranal and crocin increased CAT activity in liver tissue (Asdaq and Inamdar, 2010, Farahmand et al., 2013, Samarghandian et al., 2013), while all three constituents increased SOD levels (Asdaq and Inamdar, 2010, El-Beshbishy et al., 2012, Farahmand et al., 2013, Samarghandian et al., 2013, Shen and Qian, 2006), and glutathione availability

(Farahmand et al., 2013, Razavi et al., 2013, Samarghandian et al., 2013, Shen and Qian, 2006). Saffron and its constituents also protected against oxidative stress, evidenced by its lowering effect on markers of lipid peroxidation such MDA (El-Beshbishy et al., 2012, Farahmand et al., 2013, Samarghandian et al., 2013, Wang et al., 2012), thiobarbituric acid reactive substance (TBARS), (Ahmad et al., 2005, Sadeghnia et al., 2013, Shen and Qian, 2006), and 8-iso-prostaglandin F(2 beta) (Hariri et al., 2010).

Although safranal, crocin and crocetin each have strong antioxidant effects, it seems that their potency is greatest when delivered collectively. In a comparison on the effects of crocin only versus saffron on several antioxidant enzymes and markers of oxidative stress, both demonstrated benefits, although the effects of saffron were superior (Asdaq and Inamdar, 2010). This highlights the synergistic effects of the constituents found in saffron in ameliorating oxidative stress.

Anti-inflammatory effects

Over the past decade researchers have increasingly investigated the influence of inflammation and immune system dysregulation in major depression. From meta-analyses it has been established that depression is associated with increased C-reactive protein (Howren et al., 2009, Valkanova et al., 2013), interleukin-6 (IL-6) (Liu et al., 2012, Valkanova et al., 2013), and tumour necrosis factor-α (TNF- α) (Dowlati et al., 2010, Hiles et al., 2012, Liu et al., 2012). Anti-inflammatory actions from antidepressant medications have also been confirmed from two recent meta-analyses (Hannestad et al., 2011, Hiles et al., 2012). Further support for a role of inflammation in depression is provided by studies demonstrating significant co-morbidity between inflammatory-based diseases and major depression (e.g., cardiovascular disease, cancer, digestive diseases and post-viral infection), and the capacity of cytokine therapy for

the treatment of hepatitis C to trigger depressive symptoms (Anderson et al., 2014, Raison et al., 2006, Raison and Miller, 2011).

From investigations on crocin and crocetin, it has been confirmed that saffron has strong anti-inflammatory effects (Poma et al., 2012). In an *in vitro* study, crocin exhibited dual inhibitory activity against the cyclooxygenase-1 (COX-1) and COX-2 enzymes and inhibited the production of prostaglandin E(2) PGE(2) (Xu et al., 2009). The chemical induction of arthritis in mice elevated serum levels of TNF-α, IL-1β, nuclear factor- κB (NF-κB), IL-6, COX-2, and PGE(2), which was effectively neutralised by crocin (Hemshekhar et al., 2012). In chemically induced colitis in mice, crocin decreased the mRNA expression of TNF-α, IL-1β, IL-6, interferon- γ (IFN-γ), NF-κB, COX-2, and inducible nitric oxide synthase (Kawabata et al., 2012). Crocin and crocetin also reduced lipopolysaccharide-stimulated microglial cell production of TNF-α, IL-1β, and NF-κB activation (Nam et al., 2010).

Recent evidence suggests that saffron drives a shift toward T-helper 2 (Th2) immunity. The oral administration of alcoholic extract of saffron to mice potentiated the Th2 response of humoral immunity causing an elevation of CD19(+) B cells and IL-4 cytokine. However, saffron had no appreciable effect on the T-helper 1 (Th1) cytokines, IL-2 and IFN-γ (Bani et al., 2011). This Th2 upregulation may be particularly beneficial in depression as it is associated with an over activation of Th1 (or cell-mediated) immunity (Maes et al., 2012a).

Serotoninergic effects

Neurotransmitter imbalances are commonly cited as a primary cause of major depression, with greatest interest in the serotonergic system. Evidence of dysfunction in the serotonergic system is supported by tryptophan depletion studies which induce depressive symptoms in people with a history of depression (Hood et al., 2005, Toker et al., 2010), research demonstrating abnormalities in serotonin receptors in depressed patients (Carr and Lucki,

2011), and evidence of abnormalities in the expression of the enzyme tryptophan hydroxylase in depressed individuals (Matthes et al., 2010). Further support is also provided by the popularity and effectiveness of serotonin reuptake inhibitors (SSRIs) (Cowen, 1990, Maletic et al., 2007).

Investigation into saffron's effect on serotonin availability is limited, although this is proposed as one potential mechanism of action. Obesessive-compulsive-like behaviour in rodents in the form of excessive self-grooming was induced by the administration of meta-Chlorophenylpiperazine (mCPP), a non-selective serotonin (5-HT) receptor agonist displaying affinity for the 5-HT_{2c} family receptors. These behaviours were significantly reduced by the co-administration of crocin. These results suggest that crocins influence serotonergic mechanisms by having an antagonistic action at the 5-HT_{2c} receptor site (Georgiadou et al., 2012). The influence of saffron on serotonin availability is also indicated by its effect on premenstrual symptoms, which are theorised to be at least partly associated with the serotonergic system; however, this requires further investigation (Agha-Hosseini et al., 2008).

HPA-modulating effects

Alterations in HPA activity have long been recognised in major depression, with a significant portion of depressed patients exhibiting HPA hyperactivity and elevated cortisol levels (Pariante and Lightman, 2008). Depression is also associated with an elevated secretion of corticotrophin releasing hormone and an impairment in the negative feedback responsiveness to glucocorticoids, a phenomenon known as glucocorticoid resistance (Pace et al., 2007, Zunszain et al., 2011). An increased size and activity of the pituitary and adrenal glands is also observed in depression (Kempton et al., 2011). This HPA dysregulation influences neurotransmitter availability, oxidative stress and inflammation, and can contribute to neurodegeneration (Zunszain et al., 2011).

The investigation of saffron on HPA modulation is limited, although preliminary evidence suggests a role in lowering the HPA response to stress. In mice exposed to electroshock stress, safranal and crocin extracts prevented elevations in plasma corticosterone levels (Halataei et al., 2011, Hooshmandi et al., 2011). The injection of crocin to rats over a period of 21 days during exposure to chronic restraint stress also significantly decreased plasma levels of corticosterone (Ghadrdoost et al., 2011). In a human trial on female participants, exposure to saffron odour for 20 minutes significantly lowered cortisol levels in both the follicular and luteal phases. This was also associated with reductions in symptoms of anxiety (Fukui et al., 2011).

Neuroprotective effects

Major depression is associated with compromised neurogenesis and neuronal plasticity, and low levels of brain-derived neurotrophic factor (BDNF) is common (Duman, 2009, Lee and Kim, 2010). Alterations in growth factor expression can influence neurogenesis and can contribute to structural changes in the hippocampus, nucleus accumbens, and prefrontal cortex (Jiang and Salton, 2013). The chronic administration of several classes of antidepressants, including monoamine oxidase inhibitors, SSRIs, tricyclic agents, and serotonin noradrenaline reuptake inhibitors (SNRIs) are associated with increases in BDNF concentrations (Duman and Monteggia, 2006, Sen et al., 2008).

In two separate studies, the neuroprotective effects of saffron (Ghasemi et al., 2014) and its constituent, crocin (Vahdati Hassani et al., 2014) were examined in rats exposed to the forced swimming test. A western blot analysis showed that crocin dose-dependently increased levels of CREB (cAMP response element binding protein) and BDNF, and at higher levels elevated concentrations of VGF (a neuropeptide) in the hippocampus (Vahdati Hassani et al., 2014). An aqueous extract of saffron also increased hippocampus concentrations of

BDNF, CREB, phospho-CREB, and transcription levels of BDNF (Ghasemi et al., 2014). Crocetin also protects neurons in the cerebrocortical and hippocampus regions in rats exposed to chronic cerebral hypoperfusion (Tashakori-Sabzevar et al., 2013). Pre-treatment with safranal also protects the rat hippocampus from quinolinic acid-induced oxidative stress by lowering levels of lipid peroxidation, oxidative DNA damage and preventing decreases of hippocampal thiol redox and antioxidant status (Sadeghnia et al., 2013).

From the reviewed literature, saffron has several potential antidepressant mechanisms of action. However, as most of the studies are *in vitro* or animal-based, human-based investigations are required to better elucidate the antidepressant actions of saffron. Because plant constituents undergo significant metabolism via enzymatic and hepatic processes and have varying levels of bioavailability, *in vitro* and animal studies do not necessarily translate to human biological processes (Sarris et al., 2011). Further human-based investigations are therefore required. Also, while the reviewed antidepressant mechanisms of action of saffron have been discussed separately, they are not mutually exclusive and greater understanding of their interaction will be important.

In the subsequent sections, findings from a systematic review of clinical studies are detailed, and include a comprehensive appraisal of patient characteristics; dosages, extract sources, and standardisations used; safety profile of saffron; and length of treatment.

Methods

Information for this systematic review was compiled by the first author by searching PubMed, Google Scholar, PsycINFO and The Cochrane Library databases and by examining reference lists of relevant papers to locate additional studies that were not identified by the database searches. Databases were scanned from all years of study until April 2014.

Search strategy and eligibility criteria for clinical studies

A systematic search of controlled clinical trials using the terms "depression", "crocus", "saffron" was completed. Specific inclusion criteria for clinical studies included: (1) published in English, (2) reported randomisation strategies, (3) used double-blind controlled protocols, (4) published in peer-reviewed journals, and (5) had a placebo control or antidepressant-comparison group. When there was sufficient data from clinical trials, effect sizes as Cohen's *d* was calculated by using change in depression scores (from baseline to endpoint) and then dividing this by the standard deviation of each condition.

Quality of clinical studies

The methodological quality of studies was assessed by using the CONSORT 2010 checklist for clinical trials guidelines (Schulz et al., 2010) and by computing a Jadad score (Jadad et al., 1996).

Results

Search results

Based on the systematic search of clinical studies, a total of 17 studies were identified. Ten studies were excluded because participants did not undergo a formal diagnosis of depression or were from a non-depressed population. One study was excluded because it did not have a placebo control or antidepressant comparison group. Six studies met all inclusion criteria and were included in this systematic review. In Figure 2, the process of inclusion of studies in this review is detailed. The main characteristics of the included studies are detailed in Table 1. Of the reviewed studies, all were completed by the same Iranian research group.

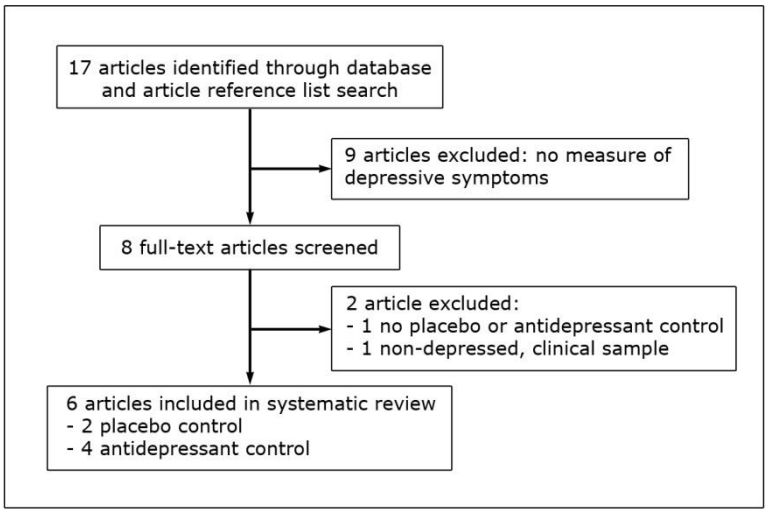

Figure 2. Process of study inclusion in systematic review

Table 1. Summary of Clinical Studies on the Antidepressant Effects of Saffron

Study	Duration	Study design	Participants	Completion rate	Depression Measures	Intervention	Control	Main Results
Akhondzadeh et al., (2005)	6 weeks	Randomised, double blind, placebo control	n = 40 Baseline HAM-D = 23 18 women & 22 men	n = 35 No difference in dropout rate between groups.	Diagnosis: SCID-IV Outcome: HAM-D	15 mg saffron (stigma), BD Standardised extract: not specified	Placebo	Greater reduction in HAM-D -17 for saffron group compared to placebo. Changes at endpoint compared to baseline were: −12.20 ± 4.67 (mean ± SD) and −5.10 ± 4.71 for saffron and placebo respectively Cohen's d effect size 1.51
Moshiri et al., (2006)	6 weeks	Randomised, double blind, placebo control	n = 40 Baseline HAM-D = 22 17 women & 23 men	n = 36 No difference in dropout rate between groups.	Diagnosis: SCID-IV Outcome: HAM-D	15 mg saffron (petal), BD Standardised extract: not specified	Placebo	Statistically significant reduction in depression HAM-D -17 compared to placebo. Changes at endpoint compared to baseline were: −14.01 ± 5.53 (mean ± SD) and −5.05 ± 4.63 for saffron and placebo respectively Cohen's d effect size 1.76
Akhondzadeh et al., (2004)	6 weeks	Randomised, double blind, antidepressant control	n = 30 Baseline HAM-D = 19 17 women & 13 men	All completed trial	Diagnosis: SCID-IV Outcome: HAM-D	10 mg saffron (stigma), TDS Standardised extract: not specified	Imipramine 100 mg/day (TDS).	Significant reduction in HAM-D-17 for both groups. No significant differences between groups.
Noorbala et al., (2005)	6 weeks	Randomised, double blind, antidepressant control	n = 40 Baseline HAM-D = 23 20 women & 20 men	n = 38 No difference in dropout rate between groups.	Diagnosis: SCID-IV Outcome: HAM-D	15 mg saffron (stigma), BD Standardised extract: 0.30-0.35 mg safranal/ capsule	Fluoxetine 10 mg BD	Significant reduction in HAM-D-17 for both groups. No significant differences between groups. Changes at endpoint compared to baseline were: −12.20 ± 4.67 (mean ± SD) and −15.00 ± 5.88 for saffron and fluoxetine respectively

Akhondzadeh Basti et al., (2007)	8 weeks	Randomised, double blind, antidepressant control	n = 40 Baseline HAM-D = 22 21 women & 19 men	n = 38 No difference in dropout rate between groups.	Diagnosis: SCID-IV Outcome: HAM-D	15 mg saffron (petal), BD Standardised extract: 0.30-0.35 mg safranal/ capsule	Fluoxetine 10 mg BD.	Significant reduction in HAM-D-17 for both groups. No significant differences between groups. Changes at endpoint compared to baseline were: −12.00 ± 4.10 (mean ± SD) and −13.50 ± 4.91 for saffron and fluoxetine respectively
Shahmansouri et al., (2014)	6 weeks	Randomised, double blind, antidepressant control	n = 40 All patients undergone PCI in the last 6 months Baseline HAM-D = 17 25 women & 15 men	All completed trial	Diagnosis: SCID-IV Outcome: HAM-D	15 mg saffron (stigma), BD Week 1: one capsule, QD every 2nd day. Week 2: one capsule, QD. Weeks 3-6: one capsule, BD Standardised extract: 0.13-0.15 mg of safranal and 1.65-1.75 mg crocin/ capsule	20 mg fluoxetine, BD Same regimen as saffron	Significant reduction in HAM-D-17 for both groups. No significant differences between groups. Changes at endpoint compared to baseline were: -11.65 ± 4.39 (mean ± SD) and -12.30 ± 3.94 for saffron and fluoxetine respectively

QD= once daily; BD = twice daily; TDS = three times daily; HAM-D -17 - Hamilton rating scale for depression; SCID-IV = structured clinical interview for DMS IV; PCI = percutaneous coronary intervention

Quality of clinical studies

The Jadad score calculated for all clinical trials was 5, indicating high-quality research designs. All clinical studies also met greater than 20 of the 25 CONSORT 2010 checklist items, further supporting high quality of trial designs.

Sample characteristics

A total of 230 adult outpatients (118 women and 112 men) diagnosed with major depressive disorder were enrolled across all studies. In all studies, major depression was diagnosed based on the structured clinical interview for DSM-IV (SCID-IV), and the Hamilton Rating Scale for Depression (HAM-D 17-item) was used as the primary outcome measure. Mean baseline HAM-D ranged from 19 to 23 indicating a moderate severity of depression. Adult participants from the ages 18 to 55 years were included in five studies. In the study by Shahmansouri et al (2014) (using participants who had received a percutaneous coronary intervention in the past year), the age of inclusion ranged from 20 to 60 years. Mean ages ranged from 34 to 37 years in five studies, except for the study by Shahmansouri et al., (2014) where the average age was 52 years. Prior to commencement in all studies, participants were free from all psychotropic medications for at least 4 weeks.

Comparison of saffron with placebo control

In two randomised, double-blind, placebo-controlled trials, saffron was effective for the treatment of mild-to-moderate depression (Akhondzadeh et al., 2005, Moshiri et al., 2006). At a daily dose of 30mg/day of *crocus sativus,* stigma or petal, a large Cohen's *d* of 1.51 (95% CI: 0.14 - 2.97) (Akhondzadeh et al., 2005) and 1.76 (95% CI: 0.26 - 3.34) (Moshiri et al., 2006) was determined.

Comparison of saffron with antidepressant treatment

When compared to antidepressant medication, reflected by four published randomised, double-blind, placebo controlled trials, saffron had similar efficacy (Akhondzadeh Basti et al., 2007, Akhondzadeh et al., 2004, Noorbala et al., 2005). In a 6-week trial, at a dosage of 30 mg/day, extracts of saffron stigma were as effective as fluoxetine (20 mg/day) for the treatment of mild-to-moderate depression (Noorbala et al., 2005). Similar findings were obtained with petal extracts of *Crocus sativus* following an 8-week trial compared to fluoxetine (Akhondzadeh Basti et al., 2007). In another trial, extracts of saffron stigma (30 mg/day) had similar antidepressant effects to imipramine (100mg/day). In a recently published randomised, double-blind study, saffron was also as effective as fluoxetine in reducing symptoms of depression in patients who had recently undergone percutaneous coronary intervention (Shahmansouri et al., 2014).

Duration of treatment

In five studies, the intervention period was 6 weeks, and in one was 8 weeks (Akhondzadeh Basti et al., 2007). Statistically significant improvements in depressive symptoms were reported after the first week, although depressive symptoms continued to subside as treatment progressed. Weekly improvements generally continued throughout the length of treatment; however, progress after 8 weeks is unknown as no long-term follow up studies have been conducted. When compared to the antidepressants imipramine and fluoxetine, saffron had a similar recovery profile over time (Akhondzadeh Basti et al., 2007, Akhondzadeh et al., 2004, Noorbala et al., 2005, Shahmansouri et al., 2014).

Dosage and standardisations

A dosage of 30mg/day delivered in two, equal doses was used in all clinical studies. As summarised in Table 1, saffron extracts standardised for crocin and/ or safranal were used in

three studies (Akhondzadeh Basti et al., 2007, Noorbala et al., 2005, Shahmansouri et al., 2014), while in the remaining three studies there were no reported standardisations for the active constituents (Akhondzadeh et al., 2004, Akhondzadeh et al., 2005, Moshiri et al., 2006). When standardisations were reported, two trials used extracts containing 0.30-0.35 mg safranal / 15 mg capsule (Akhondzadeh Basti et al., 2007, Noorbala et al., 2005) and one used 0.13-0.15 mg of safranal and 1.65-1.75 mg crocin/ 15mg capsule (Shahmansouri et al., 2014). From an examination of the magnitude of change in depressive symptoms associated with these standardised and non-standardised extracts, it seems that their treatment efficacy was comparable. In the standardised extracts there were mean reductions of 12.00 (SD = ±4.10) (Akhondzadeh Basti et al., 2007), 12.20 (SD = ±4.67) (Noorbala et al., 2005) and 11.65 (SD = ±4.39) (Shahmansouri et al., 2014) in the HAM-D. In the non-standardised extracts there were mean HAM-D reductions of 12.20 (SD = ±4.67) (Akhondzadeh et al., 2005), and 14.01 (SD = ±5.53) (Moshiri et al., 2006).

Extract source

The stigma of *Crocus sativus* have been used in 4 studies and the petal has been used in 2 studies. Efficacy rates are similar using the two extracts as indicated by mean HAM-D reductions ranging from 11.65 (SD = ±4.39) to 12.20 (SD = ±4.67) in studies using the stigma and reductions of 11.65 (SD = ±4.39) and 14.01 (SD = ±5.53) in studies using the petal.

Adverse events

Adverse events reported in the reviewed clinical trials are detailed in Tables 2 and 3. In Table 2 details of reported side effects in antidepressant-control trials (fluoxetine and imipramine) are provided, and in Table 3 adverse events reported in placebo-controlled trials are listed. The statistical significance of differences in adverse events could not be calculated across all treatment studies. However, an inspection of frequency data indicate increased

reports of sedation/drowsiness, headache, dry mouth, constipation and sexual dysfunction with antidepressant treatment compared to saffron. Compared to placebo treatment, treatment with saffron was associated with a tendency of increased reports of anxiety/ nervousness, increased appetite, nausea, and headache.

Table 2. Number of reported adverse events in saffron and antidepressant comparison trials

Adverse event	Saffron	Antidepressant control
Anxiety/ nervousness	11	15
Decreased appetite	13	11
Increased appetite	7	10
Sedation/ drowsiness	2	8
Nausea	7	9
Headache	8	13
Dry mouth	2	11
Hypomania	2	1
Constipation	3	8
Urinary retention	1	5
Sexual dysfunction	3	9
Tremor	2	9
Sweating	2	6
Heart pounding	3	2
Insomnia	3	3

Table 3. Number of reported adverse events in saffron and placebo comparison trials

Adverse event	Saffron	Placebo
Anxiety/ nervousness	7	3
Decreased appetite	6	4
Increased appetite	5	1
Sedation/ drowsiness	1	2
Nausea	7	3
Headache	6	3
Hypomania	2	1
Tremor	3	1
Sweating	2	1
Heart pounding	4	2
Stomach pain	4	2

Discussion

From the clinical studies reviewed, saffron has demonstrated efficacy for the treatment of adults diagnosed with major depressive disorder. In people with a moderate severity of depression, saffron had large treatment effects compared to a placebo and was as effective as

the antidepressants fluoxetine and imipramine. These conclusions are consistent with a recent meta-analysis completed by Hausenblas and colleagues (2013) who calculated an overall effect size of 1.62 (95% confidence interval: 1.10-2.14) for saffron supplementation versus placebo. A null effect size was also calculated in this meta-analysis for saffron supplementation versus antidepressant medication (fluoxetine and imipramine), indicating both treatments were similarly effective in reducing depressive symptoms.

Dosage and extract source: Daily doses of 30mg/day of saffron stigma or petal extract were used with treatments lasting 6 to 8 weeks. There were no differences in treatment efficacy between these two extract sources. In a study directly comparing the efficacy of stigma and petal *crocus sativus* extracts, both were equally effective in reducing depressive symptoms in adults diagnosed with major depression (Akhondzadeh Basti et al., 2008). Although the petal extract does not contain crocin, it does contain the natural flavonoid, kaempferol, which has antidepressant effects (Hosseinzadeh et al., 2007). There are significant benefits associated with utilising the petal rather than stigma, as it is less expensive and easier to obtain in larger quantities (Melnyk et al., 2010). In an animal behavioural model, an extract of saffron corms (underground plant stem) also produced antidepressant effects and presents as another potential extract source, associated with increased accessibility and lowered costs compared to stigma (Wang et al., 2010).

Standardisation and quality control: Varying standardised extracts were used in the reviewed studies. In half of the studies no standardisations were specified while in the remaining studies varying extracts standardised for safranal and crocin were used. However, standardisations did not influence treatment efficacy as mean reductions in HAM-D were similar across all studies. Despite this finding, standardisation is commonly used in herbal medicine as one measure of quality control and allows for greater comparability across studies, although as argued by Scholey et al. (2005) does not guarantee consistency. Quality

control is a significant issue in herbal medicine, highlighted by a recent study by Newmaster et al. (2013). DNA testing of 44 herbal products showed that most of the tested products were of poor quality, subjected to considerable product substitution, contamination and fillers. Given the extremely high price associated with saffron stigma and difficulties associated with its production, saffron is not immune to this problem and historically has been subject to adulteration. Natural and artificial additives such as colouring agents (e.g. ground paprika/turmeric), organic compounds (e.g. honey and oil), and inorganic compounds (e.g., borates, sulfates, chlorides, and carbonates) have been added to saffron throughout the centuries (Melnyk et al., 2010). To combat this problem and ensure its authenticity and quality, grading standards are set by the International Organization for Standardization (ISO), a federation of national standards bodies (Melnyk et al., 2010). ISO 3632 deals exclusively with saffron and establishes four grades: IV (poorest), III, II, and I (finest quality). One main measure of grade is determined by the spice's crocin content, revealed by measurements of crocin-specific spectroscopic absorbance. Greater absorbances at 440-nm light indicate greater crocin concentration, with colour grades proceeding from absorbances lower than 80 (category IV) up to 190 or greater (category I) (Alavizadeh and Hosseinzadeh, 2014, Gohari et al., 2013).

Safety of saffron: In the antidepressant-comparison trials, anti-depressant treatment was associated with trends of increases in the following adverse events; sedation, dry mouth, constipation, sexual dysfunction and tremor. In the placebo-comparison trials, saffron was associated with increased reports of anxiety, increased appetite, nausea and headache. Information on toxicology and safety reports of saffron is inconsistent. In some reports, vomiting, diarrhoea and bleeding occurred after the ingestion of 2 g of saffron, although *in vivo* animal studies have shown a very low or even non-existent toxicity of both saffron and its extracts (Melnyk et al., 2010). In a human trial, the ingestion of 200 and 400 mg of saffron for 7 days was associated with slight changes in haematological and biochemical parameters,

although these remained within the normal range and were not considered medically significant (Modaghegh et al., 2008). An investigation into the short-term safety and tolerability of crocin tablets (20mg/day) was also undertaken in healthy adult volunteers. The one-month ingestion of crocin tablets had little effect on haematological, biochemical, or hormonal parameters apart from moderately decreasing levels of amylase, mixed white blood cells and partial thromboplastin time (PTT) (Mohamadpour et al., 2013).

As saffron has shown some effect on blood coagulation and platelet aggregation in *in vitro* and *in vivo* studies (Modaghegh et al., 2008), a recent double-blind, placebo-controlled investigation was undertaken using a larger sample size. One week of treatment with 200 mg and 400 mg saffron tablets did not change plasma levels of fibrinogen, factor VII (as coagulant agent), C and S protein (an anti-coagulant agent), prothrombin time or PTT (Ayatollahi et al., 2014).

On the whole, it seems that daily doses of up to 1.5 g of saffron are generally considered safe although at dosages of 5 g and above it has been reported to have toxic effects, and is fatal at a dose of 20 g (Schmidt et al., 2007). Since the efficacious dosage for the treatment of depression (30 mg/day) is much lower than these reported levels and is in accordance with the amount of saffron used in various cuisines, there is a very large margin of safety (Hosseinzadeh and Nassiri-Asl, 2013). Given past, albeit inconsistent findings of saffron on blood coagulation and platelet aggregation, caution is warranted on the use of saffron in people with blood coagulation disorders or with people on anticoagulant medications. Symptoms of anxiety, increased appetite, nausea and headache also require further monitoring. Longer trials are also necessary to help clarify the long term safety of saffron use in depression as no study has been greater than 8 weeks.

Directions for future research

Overall, saffron presents as a promising natural option for the treatment of mild to moderate depression with initial clinical research supporting its efficacy, at least in the short-term. Current evidence indicates that it is as effective as the pharmaceutical antidepressants fluoxetine and imipramine, with a similar recovery profile over time. Further research is, however, required to clarify the mechanisms associated with this spice and its optimal treatment schedule.

While the evidence so far supports saffron as an effective antidepressant, its efficacy across varying age groups is uncertain. Studies to date have been limited to depressed populations aged between 18 and 60 years, so its efficacy and safety outside this age range is unknown. Whether effects differ in males and females has also not been investigated specifically, although the clinical studies reviewed in this paper commonly used depressed populations with approximately equal gender distributions and did not cite differing rates of efficacy. The effectiveness of saffron in patients with co-morbid mental health disorders and for the treatment of specific depression subtypes (e.g., atypical and melancholic) is also unknown. All studies to date have also been completed by the same research group, so replication in other research settings with differing sample populations will also provide greater validation for its antidepressant effects.

The potential and safety of saffron as an adjunct to pharmaceutical antidepressants is an additional area that requires investigation. Saffron has been used in conjunction with fluoxetine in two clinical trials and has been proven safe and even beneficial for the treatment of fluoxetine-induced sexual impairment (Kashani et al., 2013, Modabbernia et al., 2012). However, its use with other antidepressant classes and its ability to enhance treatment efficacy for depression has yet to be determined.

Currently, clinical outcomes have been measured through depression questionnaires, namely the HAM-D. The use of alternative depression inventories and the measurement of physiological markers associated with inflammation, oxidative stress, and neuroendocrine balance in human clinical trials will further enhance our understanding of the antidepressant mechanisms of action of saffron.

The area of herbal medicine is complicated by often considerable differences in the quality of herbs, which can affect clinical outcomes across studies (Sarris et al., 2011). Saffron is no exception as there can be considerable variability in cultivation, production and extraction (e.g., aqueous methanol, ethanol, or water) methods used. While the studies reviewed have not revealed any significant differences in outcome between the different extracts (e.g., stigma or petal; standardised or non-standardised), further investigation in this area is certainly required.

Finally, the cited studies have only used a daily dose of 30 mg/day of saffron and follow-up periods have been no longer than 8 weeks. Further research is required to determine optimal dosages and duration of treatment, and the long term efficacy and safety of this exotic spice.

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I, Professor Peter Drummond, attest that Research Higher Degree candidate, Adrian Lopresti significantly contributed the planning, literature review, write up and statistical analyses (where appropriate) to the paper/publications entitled:

1. Lopresti, A.L., Hood, S.D., Drummond, P.D. (2013) A review of lifestyle factors that contribute to important pathways associated with major depression: diet, sleep and exercise. *Journal of Affective Disorders*, 148(1):12-27. (Chapter 3)
2. Lopresti, A.L. & Drummond, P.D. (2013) Obesity and psychiatric disorders: commonalities in dysregulated biological pathways and their implications for treatment. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 45:92-9. (Chapter 3)
3. Lopresti, A.L., Hood, S.D., Drummond, P.D. (2012) Multiple antidepressant potential modes of action of curcumin: a review of its anti-inflammatory, monoaminergic, antioxidant, immune-modulating and neuroprotective effects. *Journal of Psychopharmacology*, 26(12):1512-24. (Chapter 4)
4. Lopresti, A.L., Maes, M., Maker, G.L. Hood, S.D., Drummond, P.D. (2014) Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study. *Journal of Affective Disorders*, 167, 368–375 (Chapter 5)
5. Lopresti, A.L., Maker, G. Hood, S.D., Drummond, P.D. (2014) A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 48:102–111. (Chapter 5)
6. Lopresti, A.L., Meddens, M., Maes, M., Maker, G.L., Arnoldussen, E., Drummond, P.D. (2014) Curcumin and major depression: peripheral biomarkers to predict treatment response and antidepressant mechanisms of change. *Submitted for publication* (Chapter 5)
7. Lopresti, A.L., Drummond, P.D. (2014) Saffron (Crocus Sativus) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action. *Human Psychopharmacology: Clinical and Experimental*. Accepted for publication (Appendix1)

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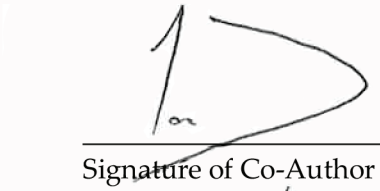

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1. Lopresti, A.L., Maes, M., Maker, G.L. Hood, S.D., Drummond, P.D. (2014) Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study. *Journal of Affective Disorders*, 167, 368–375 (Chapter 5)
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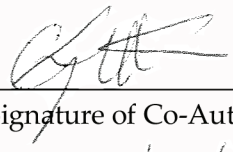

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1. Lopresti, A.L., Meddens, M., Maes, M., Maker, G.L., Arnoldussen, E., Drummond, P.D. (2014) Curcumin and major depression: peripheral biomarkers to predict treatment response and antidepressant mechanisms of change. *Submitted for publication* (Chapter 5)

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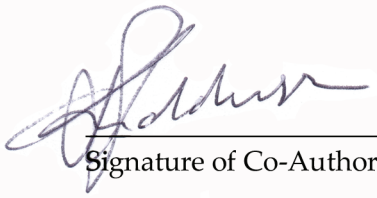
1. Lopresti, A.L., Meddens, M., Maes, M., Maker, G.L., Arnoldussen, E., Drummond, P.D. (2014) Curcumin and major depression: peripheral biomarkers to predict treatment response and antidepressant mechanisms of change. *Submitted for publication* (Chapter 5)



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Peer-reviewed journals used in publications

Journal of Affective Disorders (Impact Factor: 3.295)
The Journal of Affective Disorders is a peer-reviewed journal that publishes papers concerned with affective disorders in the widest sense: depression, mania, anxiety and panic. It is interdisciplinary and aims to bring together different approaches for a diverse readership. High quality papers will be accepted dealing with any aspect of affective disorders, including biochemistry, pharmacology, endocrinology, genetics, statistics, epidemiology, psychodynamics, classification, clinical studies and studies of all types of treatment.
http://www.journals.elsevier.com/journal-of-affective-disorders/

Progress in Neuro-Psychopharmacology & Biological Psychiatry (Impact Factor: 3.552)
Progress in Neuro-Psychopharmacology & Biological Psychiatry is an international and multidisciplinary peer-reviewed journal which aims to ensure the rapid publication of authoritative reviews and research papers dealing with experimental and clinical aspects of neuro-psychopharmacology and biological psychiatry. Issues of the journal are regularly devoted wholly in or in part to a topical subject.
http://www.journals.elsevier.com/progress-in-neuro-psychopharmacology-and-biological-psychiatry/

Journal of Psychopharmacology (Impact Factor: 3.374)
The Journal of Psychopharmacology is a fully peer-reviewed, international journal that publishes original research and review articles on preclinical and clinical aspects of psychopharmacology. The journal provides an essential forum for researchers and practicing clinicians on the effects of drugs on animal and human behavior, and the mechanisms underlying these effects. The Journal of Psychopharmacology is truly international in scope and readership. This journal is a member of the Committee on Publication Ethics (COPE)
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Human Psychopharmacology: Clinical and Experimental (Impact Factor: 2.097)
Human Psychopharmacology: Clinical and Experimental is a peer-reviewed journal that provides a forum for the evaluation of clinical and experimental research on both new and established psychotropic medicines. Experimental studies of other centrally active drugs, including herbal products, in clinical, social and psychological contexts, as well as clinical/scientific papers on drugs of abuse and drug dependency will also be considered.
http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1099-1077