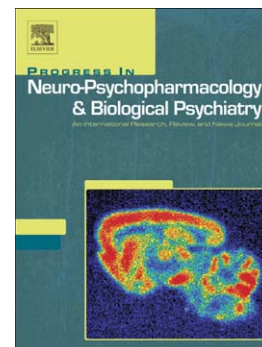# Accepted Manuscript

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

Adrian L. Lopresti, Garth L. Maker, Sean D. Hood, Peter D. Drummond

Please cite this article as: Lopresti Adrian L., Maker Garth L., Hood Sean D., Drummond Peter D., A review of peripheral biomarkers in major depression: The potential of inflammatory and oxidative stress biomarkers, *Progress in Neuropsychopharmacology & Biological Psychiatry* (2013), doi: 10.1016/j.pnpbp.2013.09.017

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

Adrian L Lopresti[1], Garth L Maker[2], Sean D Hood[3], Peter D Drummond[1]

[1] School of Psychology and Exercise Science, Murdoch University, Perth, Western Australia, 6150, Australia

[2] School of Veterinary and Life Sciences, Murdoch University, Perth, Western Australia, 6150, Australia

[3] School of Psychiatry & Clinical Neurosciences, University of Western Australia, Perth, Western Australia, 6009, Australia

Correspondence:

E: a.lopresti@murdoch.edu.au,

P: +61 0892486904

F: +61 0892484274

A: 4/ 165 Summerlakes Pde Ballajura Western Australia 6066, Australia

Word Count: 142(Abstract), 4320 (Text), 3 x Tables, **2 x Figures**

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 et al., 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 et al., 2011, Schmidt et al., 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 et al., 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 and Maes, 2012, Maes et al., 2011b, Raison and 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.

<<insert Table 1 near here>>

<<insert Figure 1 near here>>

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 et al., 2009, Valkanova et al., 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 et al., 2013), somatic symptoms (Duivis et al., 2013), depressed men with an older age of depression onset (Vogelzangs et al., 2012), depressed men in general (Elovainio et al., 2009, Ford and Erlinger, 2004, Liukkonen et al., 2011), depressed patients with a greater history of childhood adversity (Miller and Cole, 2012), and cumulative depressive episodes (Copeland et al., 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 et al., 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 et al., 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 et al., 2012b, Rybka et al., 2013) and particularly in patients suffering from melancholic symptoms (Maes et al., 2012a, 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 et al., 1998).

Erythrocyte sedimentation rate (ESR) – higher ESR was identified in depressed patients compared to healthy volunteers (Chavda et al., 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 et al., 2011a, Maes and 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 et al., 2011a, Maes and 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).

<<insert Figure 2 near here>>

<<insert Table 2 near here>>

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 et al., 2009a, Khanzode et al., 2003, Kotan et al., 2011, Ozcan et al., 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 and 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 and 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 and Miller, 2006, Jorgensen et al., 2013), and participants with recurrent episodes of depression had higher levels than those with single episodes (Forlenza and 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 et al., 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 et al., 2010) and plasma (Dimopoulos et al., 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 and Ciobica, 2012), and even greater reductions in serum SOD in patients with recurrent depression, compared to a first episode group (Stefanescu and Ciobica, 2012). However, in other studies increased RBC SOD in depressed patients were found (Bilici et al., 2001, Galecki et al., 2009a, 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 and 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 et al., 2009a) found between depressed and healthy control groups.

<<insert Table 3 near here>>

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 et al., 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 et al., 2009a). 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 et al., 2009a, Galecki et al., 2009b), 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 and 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 et al., 2009a) or 24 weeks of antidepressant treatment (Kotan et al., 2011). Galecki et al. (2009b) 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 et al., 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 et al., 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 et al., 2010, Rudnicka et al., 2007), gender (Khera et al., 2005, Lakoski et al., 2006), age (Shanahan et al., 2013, Woloshin and Schwartz, 2005), menstrual cycle (Gaskins et al., 2012, Wander et al., 2008), and BMI (Choi et al., 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 et al., 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 (Lopresti et al., 2012) and green tea (Cabrera et al., 2006, Rietveld and Wiseman, 2003), and the large array of antioxidant nutrients such as coenzyme Q_{10}, zinc, vitamin C, vitamin E and n-acetylcysteine (Ng et al., 2008, Zhang and 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 et al., 2007). The addition of biomarkers has the potential to advance a more personalised treatment approach and enhance treatment efficacy.

References

Abdel-Nasser, A. M., Abd El-Azim, S., Taal, E., El-Badawy, S. A., Rasker, J. J. & Valkenburg, H. A. Depression and depressive symptoms in rheumatoid arthritis patients: an analysis of their occurrence and determinants. Br J Rheumatol 1998;37(4):391-7.

Anderson, D. N., Abou-Saleh, M. T., Collins, J., Hughes, K., Cattell, R. J., Hamon, C. G., Blair, J. A. & Dewey, M. E. Pterin metabolism in depression: an extension of the amine hypothesis and possible marker of response to ECT. Psychol Med 1992;22(4):863-9.

Bilici, M., Efe, H., Koroglu, M. A., Uydu, H. A., Bekaroglu, M. & Deger, O. Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments. J Affect Disord 2001;64(1):43-51.

Biomarkers_Definitions_Working_Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69(3):89-95.

Boksa, P. A way forward for research on biomarkers for psychiatric disorders. J Psychiatry Neurosci 2013;38(2):75-7.

Bot, M., Carney, R. M., Freedland, K. E., Rubin, E. H., Rich, M. W., Steinmeyer, B. C. & Mann, D. L. Inflammation and treatment response to sertraline in patients with coronary heart disease and comorbid major depression. J Psychosom Res 2011;71(1):13-7.

Cabrera, C., Artacho, R. & Gimenez, R. Beneficial effects of green tea--a review. J Am Coll Nutr 2006;25(2):79-99.

Celik, C., Erdem, M., Cayci, T., Ozdemir, B., Ozgur Akgul, E., Kurt, Y. G., Yaman, H., Isintas, M., Ozgen, F. & Ozsahin, A. The association between serum levels of neopterin and number of depressive episodes of major depression. Prog Neuropsychopharmacol Biol Psychiatry 2010;34(2):372-5.

Chang, H. H., Lee, I. H., Gean, P. W., Lee, S. Y., Chi, M. H., Yang, Y. K., Lu, R. B. & Chen, P. S. Treatment response and cognitive impairment in major depression: association with C-reactive protein. Brain Behav Immun 2012;26(1):90-5.

Chavda, N., Kantharia, N. D. & Jaykaran Effects of fluoxetine and escitalopram on C-reactive protein in patients of depression. J Pharmacol Pharmacother 2011;2(1):11-6.

Choi, J., Joseph, L. & Pilote, L. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. Obes Rev 2013;14(3):232-44.

Chung, C. P., Schmidt, D., Stein, C. M., Morrow, J. D. & Salomon, R. M. Increased oxidative stress in patients with depression and its relationship to treatment. Psychiatry Res 2013;206(2-3):213-6.

Codoner-Franch, P., Navarro-Ruiz, A., Fernandez-Ferri, M., Arilla-Codoner, A., Ballester-Asensio, E. & Valls-Belles, V. A matter of fat: insulin resistance and oxidative stress. Pediatr Diabetes 2012;13(5):392-9.

Copeland, W. E., Shanahan, L., Worthman, C., Angold, A. & Costello, E. J. Cumulative depression episodes predict later C-reactive protein levels: a prospective analysis. Biol Psychiatry 2012;71(1):15-21.

Dimopoulos, N., Piperi, C., Psarra, V., Lea, R. W. & Kalofoutis, A. Increased plasma levels of 8-iso-PGF2alpha and IL-6 in an elderly population with depression. Psychiatry Res 2008;161(1):59-66.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K. & Lanctot, K. L. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010;67(5):446-57.

Duivis, H. E., Vogelzangs, N., Kupper, N., de Jonge, P. & Penninx, B. W. Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: Findings from the Netherlands Study of

Depression and Anxiety (NESDA). Psychoneuroendocrinolo 2013. http://dx.doi.org/10.1016/j.psyneuen.2013.01.002. [Epub ahead of print].

Elovainio, M., Aalto, A. M., Kivimaki, M., Pirkola, S., Sundvall, J., Lonnqvist, J. & Reunanen, A. Depression and C-reactive protein: population-based Health 2000 Study. Psychosom Med 2009;71(4):423-30.

Ford, D. E. & Erlinger, T. P. Depression and C-reactive protein in US adults: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med 2004;164(9):1010-4.

Forlenza, M. J. & Miller, G. E. Increased serum levels of 8-hydroxy-2'-deoxyguanosine in clinical depression. Psychosom Med 2006;68(1):1-7.

Gabbay, V., Klein, R. G., Katz, Y., Mendoza, S., Guttman, L. E., Alonso, C. M., Babb, J. S., Hirsch, G. S. & Liebes, L. The possible role of the kynurenine pathway in adolescent depression with melancholic features. J Child Psychol Psychiatry 2010;51(8):935-43.

Galecki, P., Szemraj, J., Bienkiewicz, M., Florkowski, A. & Galecka, E. Lipid peroxidation and antioxidant protection in patients during acute depressive episodes and in remission after fluoxetine treatment. Pharmacol Rep 2009a;61(3):436-47.

Galecki, P., Szemraj, J., Bienkiewicz, M., Zboralski, K. & Galecka, E. Oxidative stress parameters after combined fluoxetine and acetylsalicylic acid therapy in depressive patients. Hum Psychopharmacol 2009b;24(4):277-86.

Gaskins, A. J., Wilchesky, M., Mumford, S. L., Whitcomb, B. W., Browne, R. W., Wactawski-Wende, J., Perkins, N. J. & Schisterman, E. F. Endogenous reproductive hormones and C-reactive protein across the menstrual cycle: the BioCycle Study. Am J Epidemiol 2012;175(5):423-31.

Hannestad, J., DellaGioia, N. & Bloch, M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. Neuropsychopharmacology 2011;36(12):2452-9.

Herken, H., Gurel, A., Selek, S., Armutcu, F., Ozen, M. E., Bulut, M., Kap, O., Yumru, M., Savas, H. A. & Akyol, O. Adenosine deaminase, nitric oxide, superoxide dismutase, and xanthine oxidase in patients with major depression: impact of antidepressant treatment. Arch Med Res 2007;38(2):247-52.

Hestad, K. A., Tonseth, S., Stoen, C. D., Ueland, T. & Aukrust, P. Raised plasma levels of tumor necrosis factor alpha in patients with depression: normalization during electroconvulsive therapy. J Ect 2003;19(4):183-8.

Hickman, R. J., Khambaty, T. & Stewart, J. C. C-reactive protein is elevated in atypical but not nonatypical depression: data from the National Health and Nutrition Examination Survey (NHANES) 1999-2004. J Behav Med 2013. http://dx.doi.org/10.1007/s10865-013-9510-0. [Epub ahead of print].

Hiles, S. A., Baker, A. L., de Malmanche, T. & Attia, J. Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: a meta-analysis. Psychol Med 2012a;42(10):2015-26.

Hiles, S. A., Baker, A. L., de Malmanche, T. & Attia, J. A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity. Brain Behav Immun 2012b;26(7):1180-8.

Hilsenroth, M. J., Baity, M. W., Mooney, M. A. & Meyer, G. J. DSM-IV Major Depressive Episode criteria: An evaluation of reliability and validity across three different rating methods. Int J Psychiatr Clin Pract 2004;8(1):3-10.

Hoekstra, R., van den Broek, W. W., Fekkes, D., Bruijn, J. A., Mulder, P. G. & Pepplinkhuizen, L. Effect of electroconvulsive therapy on biopterin and large neutral amino acids in severe, medication-resistant depression. Psychiatry Res 2001;103(2-3):115-23.

Howren, M. B., Lamkin, D. M. & Suls, J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009;71(2):171-86.

Hrboticky, N., Leiter, L. A. & Anderson, G. H. Menstrual cycle effects on the metabolism of tryptophan loads. The American journal of clinical nutrition 1989;50(1):46-52.

Hughes, M. M., Carballedo, A., McLoughlin, D. M., Amico, F., Harkin, A., Frodl, T. & Connor, T. J. Tryptophan depletion in depressed patients occurs independent of kynurenine pathway activation. Brain Behav Immun 2012;26(6):979-87.

Iida, T., Chikamura, C., Inoue, K., Ito, Y., Ishikawa, H., Teradaira, R. & Ono, Y. Association of STAI and SDS scores with 8-hydroxydeoxyguanosine and serotonin levels in young women with depressive symptoms. J Neuropsychiatry Clin Neurosci 2011;23(1):E10.

Jorgensen, A., Krogh, J., Miskowiak, K., Bolwig, T. G., Kessing, L. V., Fink-Jensen, A., Nordentoft, M., Henriksen, T., Weimann, A., Poulsen, H. E. & Jorgensen, M. B. Systemic oxidatively generated DNA/RNA damage in clinical depression: associations to symptom severity and response to electroconvulsive therapy. J Affect Disord 2013;149(1-3):355-62.

Khanzode, S. D., Dakhale, G. N., Khanzode, S. S., Saoji, A. & Palasodkar, R. Oxidative damage and major depression: the potential antioxidant action of selective serotonin re-uptake inhibitors. Redox Rep 2003;8(6):365-70.

Khera, A., McGuire, D. K., Murphy, S. A., Stanek, H. G., Das, S. R., Vongpatanasin, W., Wians, F. H., Jr., Grundy, S. M. & de Lemos, J. A. Race and gender differences in C-reactive protein levels. J Am Coll Cardiol 2005;46(3):464-9.

Kluge, W., Alsaif, M., Guest, P. C., Schwarz, E. & Bahn, S. Translating potential biomarker candidates for schizophrenia and depression to animal models of psychiatric disorders. Expert Rev Mol Diagn 2011;11(7):721-33.

Koc, M., Karaarslan, O., Abali, G. & Batur, M. K. Variation in high-sensitivity C-reactive protein levels over 24 hours in patients with stable coronary artery disease. Tex Heart Inst J 2010;37(1):42-8.

Kodydkova, J., Vavrova, L., Zeman, M., Jirak, R., Macasek, J., Stankova, B., Tvrzicka, E. & Zak, A. Antioxidative enzymes and increased oxidative stress in depressive women. Clin Biochem 2009;42(13-14):1368-74.

Kotan, V. O., Sarandol, E., Kirhan, E., Ozkaya, G. & Kirli, S. Effects of long-term antidepressant treatment on oxidative status in major depressive disorder: a 24-week follow-up study. Prog Neuropsychopharmacol Biol Psychiatry 2011;35(5):1284-90.

Lakoski, S. G., Cushman, M., Criqui, M., Rundek, T., Blumenthal, R. S., D'Agostino, R. B., Jr. & Herrington, D. M. Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. Am Heart J 2006;152(3):593-8.

Lehtimaki, K., Keranen, T., Huuhka, M., Palmio, J., Hurme, M., Leinonen, E. & Peltola, J. Increase in plasma proinflammatory cytokines after electroconvulsive therapy in patients with depressive disorder. J Ect 2008;24(1):88-91.

Leonard, B. & Maes, M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. Neurosci Biobehav Rev 2012;36:764–785.

Liu, Y., Ho, R. C. & Mak, A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-alpha) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: A meta-analysis and meta-regression. J Affect Disord 2012;139(3):230-9.

Liukkonen, T., Rasanen, P., Jokelainen, J., Leinonen, M., Jarvelin, M. R., Meyer-Rochow, V. B. & Timonen, M. The association between anxiety and C-reactive protein (CRP) levels: results from the Northern Finland 1966 birth cohort study. Eur Psychiatry 2011;26(6):363-9.

Liukkonen, T., Silvennoinen-Kassinen, S., Jokelainen, J., Rasanen, P., Leinonen, M., Meyer-Rochow, V. B. & Timonen, M. The association between C-reactive protein levels and depression: Results from the northern Finland 1966 birth cohort study. Biol Psychiatry 2006;60(8):825-30.

Lopresti, A. L., Hood, S. D. & Drummond, P. D. Multiple antidepressant potential modes of action of curcumin: a review of its anti-inflammatory, monoaminergic, antioxidant, immune-modulating and neuroprotective effects. J Psychopharmacol 2012;26(12):1512-24.

Luukinen, H., Jokelainen, J. & Hedberg, P. The relationships between high-sensitivity C-reactive protein and incident depressed mood among older adults. Scand J Clin Lab Invest 2010;70(2):75-9.

Ma, Y., Chiriboga, D. E., Pagoto, S. L., Rosal, M. C., Li, W., Merriam, P. A., Hébert, J. R., Whited, M. C. & Ockene, I. S. Association between Depression and C-Reactive Protein. Cardiol Res Pract 2010;2011:286509.

Mackay, G. M., Forrest, C. M., Christofides, J., Bridel, M. A., Mitchell, S., Cowlard, R., Stone, T. W. & Darlington, L. G. Kynurenine metabolites and inflammation markers in depressed patients treated with fluoxetine or counselling. Clin Exp Pharmacol Physiol 2009;36(4):425-35.

Maes, M., Galecki, P., Verkerk, R. & Rief, W. Somatization, but not depression, is characterized by disorders in the tryptophan catabolite (TRYCAT) pathway, indicating increased indoleamine 2,3-dioxygenase and lowered kynurenine aminotransferase activity. Neuro Endocrinol Lett 2011a;32(3):264-73.

Maes, M., Kubera, M., Leunis, J. C., Berk, M., Geffard, M. & Bosmans, E. In depression, bacterial translocation may drive inflammatory responses, oxidative and nitrosative stress (O&NS), and autoimmune responses directed against O&NS-damaged neoepitopes. Acta Psychiatr Scand 2013;127(5):344-54.

Maes, M., Leonard, B., Fernandez, A., Kubera, M., Nowak, G., Veerhuis, R., Gardner, A., Ruckoanich, P., Geffard, M., Altamura, C., Galecki, P. & Berk, M. (Neuro)inflammation and neuroprogression as new pathways and drug targets in depression: from antioxidants to kinase inhibitors. Prog Neuropsychopharmacol Biol Psychiatry 2011b;35(3):659-63.

Maes, M., Mihaylova, I., Kubera, M. & Ringel, K. Activation of cell-mediated immunity in depression: Association with inflammation, melancholia, clinical staging and the fatigue and somatic symptom cluster of depression. Prog Neuropsychopharmacol Biol Psychiatry 2012a;36(1):169-75.

Maes, M., Mihaylova, I., Kubera, M., Uytterhoeven, M., Vrydags, N. & Bosmans, E. Increased 8-hydroxy-deoxyguanosine, a marker of oxidative damage to DNA, in major depression and myalgic encephalomyelitis / chronic fatigue syndrome. Neuro Endocrinol Lett 2009;30(6):715-22.

Maes, M., Mihaylova, I., Kubera, M., Uytterhoeven, M., Vrydags, N. & Bosmans, E. Lower whole blood glutathione peroxidase (GPX) activity in depression, but not in myalgic encephalomyelitis / chronic fatigue syndrome:

another pathway that may be associated with coronary artery disease and neuroprogression in depression. Neuro Endocrinol Lett 2011c;32(2):133-40.

Maes, M. & Rief, W. Diagnostic classifications in depression and somatization should include biomarkers, such as disorders in the tryptophan catabolite (TRYCAT) pathway. Psychiatry Res 2012;196(2-3):243-9.

Maes, M., Scharpe, S., Meltzer, H. Y., Okayli, G., Bosmans, E., D'Hondt, P., Vanden Bossche, B. V. & Cosyns, P. Increased neopterin and interferon-gamma secretion and lower availability of L-tryptophan in major depression: further evidence for an immune response. Psychiatry Res 1994;54(2):143-60.

Maes, M., Twisk, F. N. & Ringel, K. Inflammatory and cell-mediated immune biomarkers in myalgic encephalomyelitis/chronic fatigue syndrome and depression: inflammatory markers are higher in myalgic encephalomyelitis/chronic fatigue syndrome than in depression. Psychother Psychosom 2012b;81(5):286-95.

Maes, M., Verkerkc, R., Bonaccorsoa, S., Ombeletd, W., Bosmanse, E. & Scharpéc, S. Depressive and anxiety symptoms in the early puerperium are related to increased degradation of tryptophan into kynurenine, a phenomenon which is related to immune activation. Life Sci 2002;71:1837-1848.

Michalakeas, C. A., Parissis, J. T., Douzenis, A., Nikolaou, M., Varounis, C., Andreadou, I., Antonellos, N., Markantonis-Kiroudis, S., Paraskevaidis, I., Ikonomidis, I., Lykouras, E. & Kremastinos, D. Effects of sertraline on circulating markers of oxidative stress in depressed patients with chronic heart failure: a pilot study. J Card Fail 2011;17(9):748-54.

Milaneschi, Y., Cesari, M., Simonsick, E. M., Vogelzangs, N., Kanaya, A. M., Yaffe, K., Patrignani, P., Metti, A., Kritchevsky, S. B., Pahor, M., Ferrucci, L. & Penninx, B. W. Lipid peroxidation and depressed mood in community-dwelling older men and women. PLoS One 2013;8(6):e65406.

Miller, G. E. & Cole, S. W. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. Biol Psychiatry 2012;72(1):34-40.

Muller, N., Myint, A. M. & Schwarz, M. J. Inflammatory biomarkers and depression. Neurotox Res 2011;19(2):308-18.

Myint, A. M., Bondy, B., Baghai, T. C., Eser, D., Nothdurfter, C., Schule, C., Zill, P., Muller, N., Rupprecht, R. & Schwarz, M. J. Tryptophan Metabolism and Immunogenetics in Major Depression: A role for interferon-gamma gene. Brain Behav Immun 2013. http:/dx.doi.org/10.1016/j.bbi.2013.04.003. [Epub ahead of print]. 10.1016/j.bbi.2013.04.003.

Myint, A. M., Kim, Y. K., Verkerk, R., Scharpe, S., Steinbusch, H. & Leonard, B. Kynurenine pathway in major depression: evidence of impaired neuroprotection. Journal of affective disorders 2007;98(1-2):143-51.

Ng, F., Berk, M., Dean, O. & Bush, A. I. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. Int J Neuropsychopharmacol 2008;11(6):851-76.

O'Toole, S. M., Chiappelli, F. & Rubin, R. T. Plasma neopterin in major depression: relationship to basal and stimulated pituitary-adrenal cortical axis function. Psychiatry Res 1998;79(1):21-9.

Ozcan, M. E., Gulec, M., Ozerol, E., Polat, R. & Akyol, O. Antioxidant enzyme activities and oxidative stress in affective disorders. Int Clin Psychopharmacol 2004;19(2):89-95.

Pasco, J. A., Nicholson, G. C., Williams, L. J., Jacka, F. N., Henry, M. J., Kotowicz, M. A., Schneider, H. G., Leonard, B. E. & Berk, M. Association of high-sensitivity C-reactive protein with de novo major depression. Br J Psychiatry 2010;197(5):372-7.

Phillips, J., Frances, A., Cerullo, M. A., Chardavoyne, J., Decker, H. S., First, M. B., Ghaemi, N., Greenberg, G., Hinderliter, A. C., Kinghorn, W. A., LoBello, S. G., Martin, E. B., Mishara, A. L., Paris, J., Pierre, J. M., Pies, R. W., Pincus, H. A., Porter, D., Pouncey, C., Schwartz, M. A., Szasz, T., Wakefield, J. C., Waterman, G. S., Whooley, O. & Zachar, P. The six most essential questions in psychiatric diagnosis: a pluralogue part 1: conceptual and definitional issues in psychiatric diagnosis. Philos Ethics Humanit Med 2012;7:3.

Raison, C. L. & Miller, A. H. Is depression an inflammatory disorder? Curr Psychiatry Rep 2011;13(6):467-75.

Raison, C. L., Rutherford, R. E., Woolwine, B. J., Shuo, C., Schettler, P., Drake, D. F., Haroon, E. & Miller, A. H. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 2013;70(1):31-41.

Rietveld, A. & Wiseman, S. Antioxidant effects of tea: evidence from human clinical trials. J Nutr 2003;133(10):3285S-3292S.

Rosello-Lleti, E., de Burgos, F. G., Morillas, P., Cortes, R., Martinez-Dolz, L., Almenar, L., Grigorian, L., Orosa, P., Portoles, M., Bertomeu, V. & Rivera, M. Impact of cardiovascular risk factors and inflammatory status on urinary 8-OHdG in essential hypertension. Am J Hypertens 2012;25(2):236-42.

Rudnicka, A. R., Rumley, A., Lowe, G. D. & Strachan, D. P. Diurnal, seasonal, and blood-processing patterns in levels of circulating fibrinogen, fibrin D-dimer, C-reactive protein, tissue plasminogen activator, and von Willebrand factor in a 45-year-old population. Circulation 2007;115(8):996-1003.

Rybka, J., Kedziora-Kornatowska, K., Banas-Lezanska, P., Majsterek, I., Carvalho, L. A., Cattaneo, A., Anacker, C. & Kedziora, J. Interplay between the pro-oxidant and antioxidant systems and proinflammatory cytokine levels, in relation to iron metabolism and the erythron in depression. Free Radic Biol Med 2013;63C:187-194.

Sarandol, A., Sarandol, E., Eker, S. S., Erdinc, S., Vatansever, E. & Kirli, S. Major depressive disorder is accompanied with oxidative stress: short-term antidepressant treatment does not alter oxidative-antioxidative systems. Human psychopharmacology 2007;22(2):67-73.

Schmidt, H. D., Shelton, R. C. & Duman, R. S. Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. 2011;36(12):2375-2394.

Scrandis, D. A., Langenberg, P., Tonelli, L. H., Sheikh, T. M., Manogura, A. C., Alberico, L. A., Hermanstyne, T., Fuchs, D., Mighty, H., Hasday, J. D., Boteva, K. & Postolache, T. T. Prepartum depressive symptoms correlate positively with C-reactive protein levels and negatively with tryptophan levels: A preliminary report. Int J Child Health Hum Dev 2008;1(2):167-174.

Shanahan, L., Copeland, W. E., Worthman, C. M., Erkanli, A., Angold, A. & Costello, E. J. Sex-differentiated changes in C-reactive protein from ages 9 to 21: The contributions of BMI and physical/sexual maturation. Psychoneuroendocrinology 2013. http://dx.doi.org/10.1016/j.psyneuen.2013.04.010. [Epub ahead of print].

Stefanescu, C. & Ciobica, A. The relevance of oxidative stress status in first episode and recurrent depression. J Affect Disord 2012;143(1-3):34-8.

Stein, D. J., Phillips, K. A., Bolton, D., Fulford, K. W., Sadler, J. Z. & Kendler, K. S. What is a mental/psychiatric disorder? From DSM-IV to DSM-V. Psychol Med 2010;40(11):1759-65.

Sublette, M. E., Galfalvy, H. C., Fuchs, D., Lapidus, M., Grunebaum, M. F., Oquendo, M. A., Mann, J. J. & Postolache, T. T. Plasma kynurenine levels are elevated in suicide attempters with major depressive disorder. Brain, behavior, and immunity 2011;25(6):1272-8.

Swardfager, W., Herrmann, N., Dowlati, Y., Oh, P. I., Kiss, A., Walker, S. E. & Lanctot, K. L. Indoleamine 2,3-dioxygenase activation and depressive symptoms in patients with coronary artery disease. Psychoneuroendocrinology 2009;34(10):1560-6.

Theofylaktopoulou, D., Midttun, O., Ulvik, A., Ueland, P. M., Tell, G. S., Vollset, S. E., Nygard, O. & Eussen, S. J. A community-based study on determinants of circulating markers of cellular immune activation and kynurenines: the Hordaland Health Study. Clin Exp Immunol 2013;173(1):121-30.

Valkanova, V., Ebmeier, K. P. & Allan, C. L. CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies. J Affect Disord 2013. http://dx.doi.org/10.1016/j.jad.2013.06.004. [Epub ahead of print].

Vargas, H. O., Nunes, S. O., de Castro, M. R., Vargas, M. M., Barbosa, D. S., Bortolasci, C. C., Venugopal, K., Dodd, S. & Berk, M. Oxidative stress and inflammatory markers are associated with depression and nicotine dependence. Neurosci Lett 2013;544:136-40.

Vogelzangs, N., Duivis, H. E., Beekman, A. T., Kluft, C., Neuteboom, J., Hoogendijk, W., Smit, J. H., de Jonge, P. & Penninx, B. W. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. Transl Psychiatry 2012;2:e79.

Voinov, B., Richie, W. D. & Bailey, R. K. Depression and chronic diseases: it is time for a synergistic mental health and primary care approach. Prim Care Companion CNS Disord 2013. http://dx.doi.org/10.4088/PCC.12r01468. [Epub ahead of print]

Wander, K., Brindle, E. & O'Connor, K. A. C-reactive protein across the menstrual cycle. Am J Phys Anthropol 2008;136(2):138-46.

Warden, D., Rush, A. J., Trivedi, M. H., Fava, M. & Wisniewski, S. R. The STAR*D Project results: a comprehensive review of findings. Curr Psychiatry Rep 2007;9(6):449-459.

Wei, Y. C., Zhou, F. L., He, D. L., Bai, J. R., Ding, H., Wang, X. Y. & Nan, K. J. Oxidative stress in depressive patients with gastric adenocarcinoma. Int J Neuropsychopharmacol 2009;12(8):1089-96.

Wichers, M. C., Koek, G. H., Robaeys, G., Verkerk, R., Scharpe, S. & Maes, M. IDO and interferon-alpha-induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity. Mol Psychiatry 2005;10(6):538-44.

Wium-Andersen, M. K., Orsted, D. D., Nielsen, S. F. & Nordestgaard, B. G. Elevated C-Reactive Protein Levels, Psychological Distress, and Depression in 73 131 Individuals. JAMA Psychiatry 2013;70(2):176-84.

Woloshin, S. & Schwartz, L. M. Distribution of C-reactive protein values in the United States. N Engl J Med 2005;352(15):1611-3.

Yager, S., Forlenza, M. J. & Miller, G. E. Depression and oxidative damage to lipids. Psychoneuroendocrinology 2010;35(9):1356-62.

Yi, S., Nanri, A., Matsushita, Y., Kasai, H., Kawai, K. & Mizoue, T. Depressive symptoms and oxidative DNA damage in Japanese municipal employees. Psychiatry Res 2012;200(2-3):318-22.

Zhang, X. Y. & Yao, J. K. Oxidative stress and therapeutic implications in psychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry 2013. http://dx.doi.org/10.1016/j.pnpbp.2013.03.003. [Epub ahead of print].
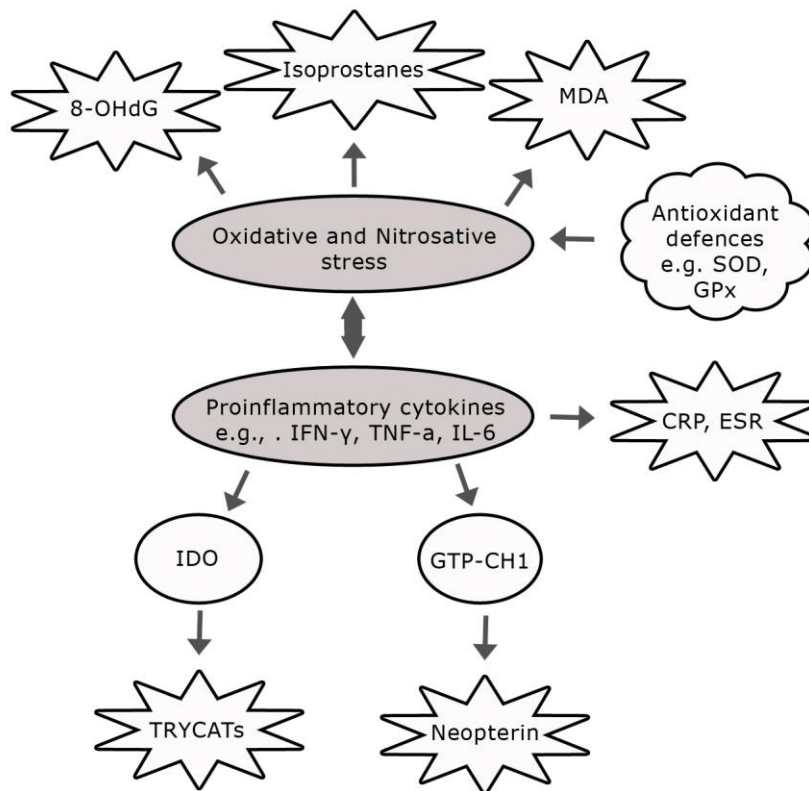
Figure 1. Pathways associated with oxidative stress and inflammatory biomarkers in major depression. Elevated pro-inflammatory cytokines (e.g, IL-6, TNF-α, and IFN-γ) upregulate the production of enzymes indoleamine 2,3 dioxygenase (IDO) and GTP cyclohydrolase I (GTP-CH1), leading to increased production 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.
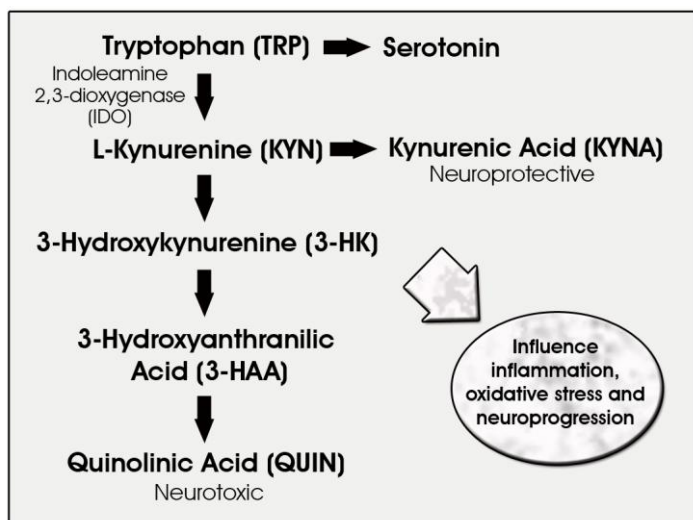
Figure 2. TRYCATs pathway. The TRYCATs pathway starts with the degradation of tryptophan by the enzyme, indoleamine 2,3-dioxygenase (IDO) which is upregulated by pro-inflammatory cytokines (e.g. IFN-γ, TNF-α, IL-, IL-6). These TRYCATS have neuroprotective and neurotoxic effects on the CNS and influence monoaminergic transmission.

Table 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.

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		Reference
			KYN	KYN/TRP Ratio	KYNA	KYNA/KYN ratio	
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		Reference
			KYN	KYN/TRP Ratio	KYNA	KYNA/KYN ratio	
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. (2011a)
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)

Population	Sample used	Tryptophan	IDO activity		Neuroprotection		Reference
			KYN	KYN/TRP Ratio	KYNA	KYNA/KYN ratio	
Depressed inpatients; healthy controls	Morning serum after overnight fast	↓ depressed than controls	↑ in depressed than controls	↑ in depressed than controls			Myint et al (2013)

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., (2009a)
	↓ whole blood	Maes et al., (2011c)
	= 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

Highlights

- Inflammation and oxidative stress are associated with major depression
- Peripheral biomarkers may aid diagnosis and predict future onset of depression
- Peripheral biomarkers may enhance treatment-matching in depression