Exploring Depression
It’s many forms & their solutions
2017

Brought to you by FxMed
Depression is...

- 'Depression' is characterised by feelings of helplessness, hopelessness, inadequacy, and sadness. However these are symptoms of several disorders and can also occur in normal individuals (Wolman 1973).
- A clinical diagnosis of depression must be accompanied by a range of other symptoms including:
  - Loss of interest of pleasure
  - Significant dietary changes
  - Sleep disturbance
  - Psychomotor changes
  - Reduced energy or tiredness
  - Sense of worthlessness
  - Impaired ability to concentrate & make decisions

What Else Could It Be?

- Grief
- Loss of meaning
- Recreational Drugs
- Anaemia
- GIT Infections or Parasites
- Peri or Menopausal
- Adrenal or Thyroid disorders
- Hypoglycaemia
- Heavy Metals
- Sleep Apnoea
- Neuro-degenerative
Depression is...

- A possible feature of many different psychiatric disorders including
  - Bipolar disorder
  - Eating disorders
  - Borderline Personality Disorder
  - Psychotic depression
  - Addiction
  - A comorbidity
  - Major Depressive Disorder, Dysthymic disorder & Depressive disorder* (Unipolar)

- Something that needs to be assessed and diagnosed by a psychiatrist (ideally) or a good GP

Unipolar Depression is many things to many different people

- Culture
- Age
- Socioeconomic status
- Education
- Religious beliefs
Traditional Models of Depression

Endogenous depression
- ‘Genetic’
- No apparent precipitating cause

Exogenous depression
- ‘Social’
- Precipitated by a stressful event

More Contemporary Ideas! (Gathercole, M 2013.
www.depressionet.org.au)

Individual Vulnerability
- Biological
- Developmental
- Coping Skills

Environmental Toxicity
- Loss
- Existential
- Context
Current Medical Approach to Depression

- Even though there is acknowledgment of the Bio-psycho-social model – medical treatment overwhelmingly focuses on the biological:
  - Pharmacological
    - SSRIs, SNRIs, serotonin agonists, melatonin X, TCAs, MAOIs
  - ECT
  - Ultraviolet Light Therapy
  - Psychodynamic Approaches
  - CBT

BUT WAIT! WHAT’S THIS??

Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders

Gin S Malhi1,2, Darryl Bassett3,4, Philip Boyce5, Richard Bryant4, Paul B Fitzgerald2, Kristina Fritz6, Malcolm Hopwood1, Bill Lyndon1,2,1,2, Roger Mulder1,2, Greg Murray1, Richard Porter1,2 and Ajeet B Singh1,2

Copyright Rachel Arthur 2017. All rights reserved. This document is provided to the purchaser for their individual professional use and may not be copied or distributed without the prior written permission of Rachel Arthur.
Figure 6. Management of major depressive disorder

GOAL
The main outcomes of treatment is the complete remission of depression with full functional recovery and the development of resilience.

STEP 0
- Taper and cease any agents that can potentially lower mood
- Implement appropriate lifestyle changes e.g. smoking cessation, regular exercise and achieve a healthy diet
- Address substance misuse and dependence

IF STEP 0 INSUFFICIENT
- Implement psychological services e.g. counseling, therapy
- Medication management
- Address underlying issues

GENERIC PSYCHOSOCIAL INTERVENTIONS
- Psychoeducation (family, friends, caregivers)
- Low intensity interventions e.g. internet based education
- Formal support groups, community groups
- Employment, housing

FORMULATION-BASED INTERVENTION
- Cognitive Behavioral Therapy (CBT)
- Interpersonal therapy
- Acceptance and Commitment Therapy
- Mindfulness-Based Cognitive Therapy

PSYCHOLOGICAL THERAPY
- Frontline
  - SSRI, SNRI, NDRIs
  - monotherapy, mirtazapine, serotonin reuptake inhibitor
- Second line
  - Tricyclic antidepressants, MAOIs

PHARMACOTHERAPY
- Frontline
  - SSRI, SNRI, NDRIs
- monotherapy, mirtazapine, serotonin reuptake inhibitor
- Second line
  - Tricyclic antidepressants, MAOIs

STEP 1
- Combine pharmacotherapy and psychological therapy
- Increase dose of antidepressant medication
- Augment antidepressant medication with lithium and/or antipsychotic medication
- Combine anticonvulsants

IF STEP 1 INSUFFICIENT
- Blood pressure, weight, fluid intake, nutrition
- Laboratory tests, electrocardiogram
- Urgent symptoms

STEP 2
- Combine pharmacotherapy and psychological therapy
- Increase dose of antidepressant medication
- Augment antidepressant medication with lithium and/or antipsychotic medication
- Combine anticonvulsants

IF STEP 2 INSUFFICIENT
- Electroconvulsive therapy (ECT)

Table 9. Physical examination and investigation of patients presenting with mood disorders.

Diagnosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual symptoms</td>
<td>Blood pressure may be altered by certain psychiatric medications and anxiety (tachycardia) may occur in high doses</td>
</tr>
<tr>
<td>Body mass index and waist circumference</td>
<td>To assess current general health status and guide subsequent psychiatric assessment and weight gain</td>
</tr>
<tr>
<td>Signs of possible malnourishment</td>
<td>Old times (including starvation)</td>
</tr>
<tr>
<td>Delirium symptoms</td>
<td>Delirium (hypertension/delirium)</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>Obstructive sleep apnea, restless leg syndrome, COPD, pneumonia, asthma, sleep apnea</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>Parkinson’s disease, cerebrovascular disease, stroke, encephalitis</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Osteoporosis, AVK for sealed, dehydrated, peripheral edema</td>
</tr>
</tbody>
</table>

Investigation

<table>
<thead>
<tr>
<th>Test</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood examination (FBE)</td>
<td>Some symptoms are associated with neoplasms and autoimmune disorders</td>
</tr>
<tr>
<td>Urine and electrolytes (UE + U&amp;E)</td>
<td>Psychiatric medications may influence by other causally related renal or hepatic impairment</td>
</tr>
<tr>
<td>Liver function tests (LFTs)</td>
<td>Possibility of hyperglycemia in elderly patients on psychiatric medication</td>
</tr>
<tr>
<td>Electrocardiogram (ECG)</td>
<td>Some symptoms are associated with a prolonged QTc interval</td>
</tr>
<tr>
<td>Thyroid function tests (TFTs)</td>
<td>Thyroid dysfunction can cause changes in mood</td>
</tr>
<tr>
<td>Serum electrolytes</td>
<td>Thyroid dysfunction can be induced by treatment such as lithium</td>
</tr>
<tr>
<td>Parasite stool</td>
<td>Need assessment on a case by case basis</td>
</tr>
<tr>
<td>Sexually Transmitted Disease (STD) testing</td>
<td>History suggests inappropriate unprotected behavior with sexual activity</td>
</tr>
<tr>
<td>Pregnancy testing (beta HCG)</td>
<td>History suggests inappropriate unprotected sexual activity</td>
</tr>
<tr>
<td>Urine and Blood Drug Screening</td>
<td>Screen for buprenorphine, opioids, psychostimulants, cannabinoids, hallucinogens</td>
</tr>
</tbody>
</table>
AN OVERVIEW OF THE ROLE NUTRITION & LIFESTYLE PLAY GENERALLY

General lifestyle factors: mental health problems

- **Disordered eating practices**
  - Overeating
  - Under-eating
  - Unhealthy food choices

- **Drugs**
  - Side effects, including drug/nutrient/herb interactions
  - Caffeine, Alcohol & Nicotine – The Big 3!

- **Physical activity – loss of**
- **Rest & sleep**
- **Time spent outdoors in sunlight**
- **Circadian rhythms**
- **Support**
**Basic Healthy Diet & Lifestyle**
- Regular food
- Healthy choices
- Balanced blood sugar
- Exercise

**Correct Nutritional Deficiencies & Excesses**

**Nutritional treatment of additional Depression drivers**
e.g. methylation, monoamine imbalance

**Nutritional treatment of comorbidities**
e.g. thyroid disorders, cardiovascular disease

**Address Drug Nutrient Interactions**
- Recreational drugs
- Medications

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Class</th>
<th>Main Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin (SHT)</td>
<td>Indolamines (Monoamine)</td>
<td>Inhibitory</td>
<td>Involved in many functions, including mood, appetite, sleep and self-esteem. Vascular function, platelets, digestive function.</td>
</tr>
<tr>
<td>Dopamine (DOP)</td>
<td>Catecholamine (Monoamine)</td>
<td>Excitatory</td>
<td>Involved in movement, motivation and emotion. Produces feelings of pleasure when released by the brain’s reward system, also involved in learning.</td>
</tr>
<tr>
<td>Adrenergic:</td>
<td></td>
<td></td>
<td>Strong influence in sympathetic nervous system (flight/fight). CNS- alertness, learning and decision making, mood. Receptors α1, α2, β.</td>
</tr>
</tbody>
</table>

Noradrenaline (NAD), Adrenaline (AD)

Copyright Rachel Arthur 2017. All rights reserved. This document is provided to the purchaser for their individual professional use and may not be copied or distributed without the prior written permission of Rachel Arthur.
<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Class</th>
<th>Main Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate (GLU)</td>
<td>Amino Acid</td>
<td>Excitatory</td>
<td>Most common neurotransmitter, released in more than 90% of the brain’s synapses.</td>
</tr>
<tr>
<td>Gamma-aminobutyric acid (GABA)</td>
<td>Amino Acid</td>
<td>Inhibitory</td>
<td>Major inhibitory neurotransmitter in the brain</td>
</tr>
<tr>
<td>Histamine (HIS)</td>
<td>Indolamines</td>
<td>Excitatory</td>
<td>Sleep and appetite suppression. Plays role in chemotaxis and stimulating gastric excretions. Decreases release of histamine (self regulating), acetylcholine, norepinephrine, serotonin.</td>
</tr>
<tr>
<td>Melatonin (MT)</td>
<td>Indolamines</td>
<td>Inhibitory</td>
<td>Powerful antioxidant neurohormone involved in the circadian rhythm and regulation of other hormones.</td>
</tr>
</tbody>
</table>

METHYLATION MODEL
Methylation Model

Hypothesis
Some depressed patients have impaired methylation resulting in altered phospholipid, monoamine and neurotransmitter synthesis in addition to possible accumulated homocysteine (Hcy) levels which have established neurotoxic properties.
The Methylation Model

Treatment

- Assess possible nutritional deficiencies contributing to impaired methylation and correct with supplementation
- Reduce elevated homocysteine (Hcy) levels

Methylation Model

- What dietary & lifestyle choices could produce impaired methylation in an individual?

- Inadequate intake folate, B12, B6
- Inadequate B2!
- Use of medications that act as folate antagonists or impairs levels of other methyl donors
- Genetic Polymorphisms
- Low stomach acid, damage to SI lining
- High alcohol intake
- Net inflammatory – pro-oxidant state
A case for Folate

- Key methyl donor
- Appearance of neuropathology occurs early in deficiency of this vitamin
- Deficiency produces increased Hcy
- Involved in neurotransmitter synthesis
- High rates of folate deficiency observed in psychiatric population
- Identification of below the median dietary folate consumption (<256 mcg/d) and a MTHFR C677T genotype (polymorphism) as independent risks for depression
The prevalence of Folate deficiency in depressed patients

- Overall, it has been estimated that between 15-38% of depressed people also have a folate deficiency (Alpert & Fava 1997)

- Over the past three decades, numerous studies have identified an association between folate deficiency and symptoms of depression and cognitive decline, particularly in psychiatric and geriatric populations (Reynolds 2002).

- “In medical patients psychiatric symptoms occur more frequently, and in psychiatric patients symptoms are more severe, in those with folate deficiency than in those with normal levels.” (Young & Ghadirian 1989).

A case for $B_{12}$

- Neuropathology central to deficiency picture of this vitamin

- Deficiency produces increased Hcy

- Key methyl donor

- Essential for the actions also performed by folate

- Moderately high rates of deficiency in the community particularly amongst at risk groups
The prevalence of $B_{12}$ deficiency in depressed patients

- Up to 30% of patients hospitalized for depression exhibit $B_{12}$ deficiency according to observational studies (Hutto).
- Other researchers agree that elevated $Hcy$ accompanied by $B_{12}$ deficiency is a common finding in MDD patients (Coppen and Bolander-Gouaille 2005)
- A study of 700 physically disabled women >65 years demonstrated that those with a $B_{12}$ deficiency had a twofold risk of depression

EVIDENCE OF EFFICACY – THE METHYL DONORS
Response to Antidepressants – the impact of Folate status
(Alpert et al. 2003; Papakostas et al 2004; Papakostas et al. 2005)

<table>
<thead>
<tr>
<th></th>
<th>Folate Replete</th>
<th>Folate Deficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Time</td>
<td>3 wks</td>
<td>Delay ≤ 1.5wks</td>
</tr>
<tr>
<td>Response Rate</td>
<td>44.7%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Relapse Rate</td>
<td>3.2%</td>
<td>49.2%</td>
</tr>
</tbody>
</table>

Update on Folate in Depression

- Earlier trials reported marked positive effects with synthetic folic acid in large doses
- More recent studies & reviews suggest clinical superiority of active forms such as methylfolate (Sarris et al 2016)
- However while original studies were conducted particularly on folate deficient individuals which produced good results, more recent studies have administered folate regardless of the subjects baseline folate status
- Very few studies have also taken into account MTHFR polymorphisms of the subjects
- This has resulted in poorer trial outcomes for folate treatment of depression but this is likely to be an artefact
Update on Folate as an Intervention in Depression

- Future research should be more sophisticated & only use folate in those individuals who are deficient and/or effected by MTHFR polymorphisms.
- A better example is an observational study of pregnant women given folic acid or placebo and followed up over 21mo post-partum to assess if supplementation reduced the risk of developing post-partum depression.
- While folic acid supplementation was not associated with depression scores generally across the sample, there was a particularly strong protective effect against subsequent development of PPD for those women with the most severe folate polymorphism: C677T homozygotes. (Lewis et al 2012)

Who might benefit from Folate?

- Low dietary intake
- Primary or secondary hypo or achlorhydria
- Coeliac, Crohn’s disease
- HIV
- Pregnant & lactating women
- *Patients with malignancies*
- Haemolytic anaemias
- Chronic exfoliative skin disorders e.g. psoriasis?
- Haemodialysis patients
- Hemochromatosis patients
Who might benefit from Folate?

- Low rbc (<1000) or serum folate (<25)
- High rbc folate & serum B₁₂ in unsupplemented individual
- Elevated fasting Hcy (>8 mmol/L)
- Use of folate depleting medication e.g. anti-convulsants, immune suppressants, PPIs, sulfasalazine
- Excessive alcohol intake
- Hx of recurrent spontaneous abortion, offspring with congenital defects including NTD

Who Might Benefit from Folate?

- Suspected (FHx) or confirmed MTHFR polymorphisms?
Various MTHFR polymorphisms & their impact on enzyme activity (Gilbody et al 2008, Lynch 2013)

- Individuals carrying **1 copy** of the **C677T polymorphism** exhibit **35% less activity**
- Individuals carrying **2 copies** of the **C677T polymorphism** exhibit the **70% less activity**
- Individuals carrying **1 copy** of the **A1298C polymorphism** exhibit **20% less activity**
- Individuals carrying **2 copies** of the **A1298C polymorphism** exhibit **40% less activity**
- Individuals carrying **1 copy of the C677T mutation & 1 copy of the A1298C mutation** (called a compound heterozygote) exhibit **40-50% less activity**
### MTHFR Links with Depression?

<table>
<thead>
<tr>
<th>SNP</th>
<th>No. of copies</th>
<th>↓ in MTHFR activity</th>
<th>Odds Ratio</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C677T</td>
<td>1</td>
<td>35%</td>
<td>1.10</td>
<td>Gilbody et al 2008</td>
</tr>
<tr>
<td>C677T</td>
<td>2</td>
<td>70%</td>
<td>1.36</td>
<td>Gilbody et al 2008</td>
</tr>
<tr>
<td>A1298C</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>Reif et al 2005 cited Peerbooms et al 2011</td>
</tr>
<tr>
<td>A1298C</td>
<td>2</td>
<td>40-50%</td>
<td>2.63*</td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>Heterozygote</td>
<td>50%?</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>
Would the association be stronger if we factored in the gene-environment interaction? (Lok et al 2013)

- 124 individuals over 5.5 years who suffered with recurrent depression
- Individuals were genotyped and also assessed for exposure to childhood trauma
- Researchers found a strong significant association between homozygous C677T mutation, the experience of childhood trauma and depression recurrence

<table>
<thead>
<tr>
<th>Homozygous C677T MTHFR</th>
<th>Childhood trauma</th>
<th>Median time to recurrence of depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Y</td>
<td>461 days</td>
</tr>
<tr>
<td>Y</td>
<td>Y</td>
<td>191 days</td>
</tr>
</tbody>
</table>
Clinical Applications of Folate

- **Therapeutic doses used in trials:** 5-50mg/d of FA or methyl-tetrahydrofolate (MTHF) or to a lesser extent folinic acid (FOL)
- **Therapeutic doses in clinic:** 1-5mg/d of FOL or 5MTHF
- **Response Time:** Variable
- **Side effects:** Adverse reactions appear to be limited to oral doses > 5mg/day. Reactions include a generalised urticaria associated with an allergic response, nausea, flatulence and bitter taste in the mouth, irritability and excitability which are all reversible upon stopping supplement.

Cautions and Contraindications:

- Caution when prescribing high dose without concurrent B12, risk of masking pernicious anaemia in susceptible individuals
- Caution with high dose use of *folic acid* form – questions over safety
- ✗ Contraindicated in conjunction with drugs whose action is dependent upon folate antagonism e.g. methotrexate – check with GP/specialist
B₁₂ trials

- One study of 115 clinically depressed patients revealed a possible causal relationship between good B₁₂ status and better treatment response to orthodox treatment (Hintikka et al. 2003).

Presentations suggestive of a B₁₂ Issue

- Vegetarian or vegan diet
- Hypo/achlorhydria either primary or secondary
- Gastric of small intestine surgery
- Pancreatic insufficiency
- Abnormal small intestine gut flora
- Coeliac or Crohn’s disease
- Radiation damage
Presentations Suggestive of B\textsubscript{12} Issue

- Ambiguous Serum B\textsubscript{12} (<400pmol/L)
- Low Active B\textsubscript{12} (<60 pmol/L)
- Elevated fasting Hcy (>8 mmol/L)
- Suboptimal blood MMA (< 0.35 µmol/L)
- Presence of B\textsubscript{12} related antibodies
- Use of B\textsubscript{12} depleting medication e.g. anti-convulsants, PPIs
- Excessive alcohol intake

Clinical Applications of B\textsubscript{12}

Therapeutic doses used in trials & clinic:

6-400mcg/ day (typical dose 1000 µg/day) consider sublingual & IM when B12 uptake questionable

Response time: 6wks – 9wks

Side effects:

No reported side effects with oral doses up to 2000µg per day (Kuzminski et al. 1998).
Clinical Applications of B<sub>12</sub>


- Unclear! But there are numerous plausible mechanisms at play including:
  - Increased levels of **noradrenaline and serotonin** in brain
  - General shift towards increased monoamine synthesis
  - Augmentation of **dopaminergic activity**
  - Decreased prolactin secretion
  - Improved cell membrane structure & fluidity
  - Influence on expression of **genes** affected behaviour, learning, mood etc.
  - **Neurotrophic effects**
  - Reduced oxidative stress, improved GSH levels
  - Improved histamine turnover?
**SAMe in Depression – Runs on the Board as Stand Alone Tx** (Mischoulon et al 2012, Papakostas et al 2010, Sarris et al 2014)

- 6 RDBPCT using SAMe parenterally (IM)
- 3 RDBPCT using SAMe orally V antidepressants in MDD
- 3 RDBPCT using SAMe orally V placebo in MDD
- Generally small sample size

**Meta-analysis however confirms comparable efficacy at least with pharmaceutical antidepressants**

- E.g. in most recent study comparing SAMe to citalopram (Sarris et al 2014)
  - SAMe was superior to placebo in reducing depression at wk 1
  - SAMe was superior to citalopram at wks 2,4 & 6
  - Response rate for SAMe 45% V citalopram 26%
  - Remission rate for SAMe 34% V citalopram 23% V placebo 6%


- SAMe has been investigated in a few studies in combination with pharmaceutical antidepressants for non-responders
- Oral doses have ranged from 800mg to 1600mg/d
- General findings have been reduced latency time of the antidepressant, which means faster onset of action
- Improved response rates compared to the antidepressant on its own
- Reduced incidence of antidepressant side effects esp. sexual

“Although SAMe seems more expensive, considering its side-effects profile and its rapidity of onset of the antidepressant effect, it may have a specific impact on the use of resources in terms of drug acquisition, treatment duration and dosage, inpatient and outpatient care, treatment of adverse events, management of patients who discontinue therapy and time off work.”

Galizia et al S-adenosyl methionine (SAM-e) for depression in adults (Protocol) 2014 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.
Who Might Benefit from SAMe?

- Evidence of methylation issues but patient is not responsive or aggravates on folate
- ‘High histamine’ types
  - Competitive & driven
  - Perfectionistic
  - Anxious
  - Difficulty with sleep onset
  - Tendency to be slim body type
  - Propensity for ‘allergies’
- Patients with Gilbert’s Syndrome and elevated bilirubin

Clinical Applications of SAMe

- Therapeutic doses used in trials & clinic:
  Mild depression 400-600mg/day
  Moderate-severe 800-1,600mg/day (Mischoulon 2002).
- Response time: Within 10 days (Salmaggi et al. 1993).
- Side effects: 2 yr post-marketing survey of 20,461 patients conducted in Germany: 80% reported that they were without side effects, 20% complained of mild side effects for first - all pts on the doses >1gm per day (Brown 2000)
- Cautions & Contraindications:
  - Is capable of inducing mania in susceptible individuals - should not be used in bipolar disorder
  - Safety in pregnancy uncertain
Diane 64yo

- First presented in 2012 with extremely severe anxiety & depression
- Anxiety most extreme on waking
- Had long history of frequent depressive episodes which had increasingly become more treatment resistant
- Current episode had begun 3mo prior, she had trialled numerous medications & had not tolerated or aggravated on each one
- Now advised ECT only option

While observing a safe drug withdrawal period started her initially on methionine 1g BD, taurine 1g TIDS, Magnesium, Vitamin C & Zinc

- Regular food intake & avoidance of all caffeine
- High am cortisol 541 pmol/L
- Histamine 0.6 µmol/L
- Hcy 6.5
- Biochemical markers of magnesium & potassium deficiency
- Within 2 weeks – only improvement seemed to be attributable to full withdrawal from TCA
Diane 64yo

- Started her on SAMe 400mg and titrated up to 800mg/d within 1 week
- Reports significantly reduced mania/drive/anxiety with starting SAMe
- After 6mo reduced dose to 400mg/d → ongoing
- DASS reassessed on a regular basis – no anxiety/depression/no relapse
**Dysglycaemia Model**

**Hypothesis**

Impaired BGL management and/or Chromium deficiency

a) Interferes with Tryptophan delivery to the brain therefore potentially compromising 5HT production

b) Exposes the brain to high BGL which in turn can precipitate oxidative stress

c) Secondary decreased cell membrane fluidity due to over-accumulation of cholesterol

d) Direct effects upon 5HT levels & activity

e) Is a primary driver of ‘hypofunction’ of the cortex esp.

**Evidence**

- Established relationship between diabetes and depression.
- Individuals diagnosed with one are at an increased risk of developing the other
- Chromium supplementation has been shown to be most effective in reducing depressive symptoms (70% response rate & 50% reduction in symptoms from baseline) for those individuals with pronounced carbohydrate craving and over-eating features which are present in ‘atypical depression’
Dysglycaemia

- What diet & lifestyle choices could produce this effect in an individual?

- High GI Diet
- Inadequate Chromium
- Obesity – especially central
- Secondary damage to glucose transporters e.g. cocaine
- Impaired Insulin via low Zn, Mg, Lipoic
- High cortisol environment
- Irregular eating patterns, inadequate protein intake

Prevalence of diabetes and impaired glucose tolerance in patients with schizophrenia

Oncologic, Endocrine & Metabolic

The effect of antidepressants on glucose homeostasis and insulin sensitivity: synthesis and mechanisms

Roger S Melaniya, Joanna K Szczyńska, Jakub Z Konarski, & Sidney H Kennedy

Objective: To synthesise results from investigations reporting on the effect of antidepressants on glucose–insulin homeostasis. Method: The authors conducted a MedLine search of all English language articles from 1966 to October 2005 using the keywords: bipolar disorder, major depression disorder, diabetes mellitus, glucose homeostasis, and the name of each antidepressant that has been indicated for major depression in Canada and the US up to October 2005. The search was supplemented with a manual review of relevant references. Both preclinical and clinical investigations were reviewed. Results: Some serotonin and noradrenergic antidepressants (e.g., fluoxetine) reduce hyperglycaemia, normalise glucose homeostasis and increase insulin sensitivity, whereas some noradrenergic antidepressants (e.g., desipramine) exert opposite effects. Dual-mechanism antidepressants (e.g., duloxetine and venlafaxine) do not appear to disrupt glucose homeostatic dynamics, whereas nonselective hydrazine monoamine oxidase inhibitors (e.g., phenelzine) are associated with hypoglycaemia and an increased glucose disposal rate. Conclusion: Some antidepressants exert a clinically significant effect on metabolism relevant to both therapeutic outcome and adverse events.
Who Might Benefit from Correction of Dysglycaemia?

- Marked CHO craving or hyperphagia especially at night time
- Poor dietary patterns & behaviour
- Tendency to hypersomnia
- May have central adiposity but often doesn’t
- ‘Elevated’ FBGL – seems disproportionate for individual
- ‘Elevated’ fasting lipids esp TGs – as above
- Also patients with a bipolar depression or schizophrenia diagnosis

49yo Severe Anxiety & Depression – Slim & Fit

<table>
<thead>
<tr>
<th>Glucose Fasting</th>
<th>Status</th>
<th>Insulin - Serum</th>
<th>Fasting</th>
<th>14</th>
<th>mU/L</th>
<th>5.5 H</th>
<th>mmol/L</th>
<th>(&lt;5.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>4.8</td>
<td>mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>2.5</td>
<td>mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>1.3</td>
<td>mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol/HDL Ratio</td>
<td>3.7</td>
<td>mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non HDL-Cholesterol</td>
<td>3.5</td>
<td>mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>2.4</td>
<td>mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A Case for Chromium
(Iovieno et al 2011)

Animal studies
- Chromium supplementation in rats has resulted in improved modified forced swimming tests that are indicative of a serotonergic antidepressant action and also provide preliminary evidence of an anxiolytic effect

Case reports & RCTs
- Rapid (4d - 2wks) reduction or remission of depression when used as a stand alone treatment or adjuvant to sertraline in SSRI refractory patients.

Clinical application of Chromium

Therapeutic doses in trials & clinic:
- 400 – 600 mcg of CrPic supplemented over 8 wks (Docherty et al. 2005; Davidson et al. 2003; Stewart et al. 2007)
- Many researchers have concluded, however that higher doses (e.g. 1mg Cr) may be indicated for increased success (Docherty et al. 2005; Stewart et al. 2007)
- Consider adding in a serotonergic agent when necessary

Response time: 4d-2wks

Side effects: Initial insomnia & vivid dreaming (take away from bedtime), tremor & psychomotor retardation have been reported. (Iovieno et al 2011)

High doses (>1mg) of Cr picolinate in an HIV+ population have resulted in raised LFTs which resolved upon cessation of supplement
A Case for HPA axis Dysregulation
(Krishnan & Nestler 2010, Brummelte & Galea 2009)

- A large amount of evidence supports the theory that stress induced hypercortisolemia → central down-regulation of glucocorticoid receptors → impaired cortisol negative feedback → elevated CRH & ACTH → chronic hypercortisolemia

- Aka – the volume dial is broken & my stress stereo is stuck on DEAFENING!

- Chronically elevated cortisol does produce hippocampal atrophy, altered circadian rhythms, reduced neurogenesis & impaired cognition all seen in depression…. BUT
A Case for HPA axis Dysregulation

- High cortisol does not fit with the inflammatory aspects of depression if the wcc GR are working properly nor with every individual’s clinical picture of their depression
- Consider this
  - Perhaps some HPA dysregulation results in hypercortisolemia producing classic features such as insomnia, hypophagia etc. (melancholic features)
    - Consider also possibility of suppressed immunity and IR
  - And in other individuals produces hypocortisolemia resulting in the fatigue and hyperphagia (atypical features)
    - Consider the possibility of pronounced inflammation and difficulty maintaining BGL e.g. ‘sleepfeeders’

What’s Behind High Cortisol?

- Is this secondary to another driver? e.g.
  - broken HPA axis with impaired feedback inhibition
  - stress perception (behaviour) including over-stimulation
  - allergy (could → low cortisol over time)
  - BGL imbalance, excessive ‘fasting’
  - physiological acidity
  - high histamine
  - Cushing’s syndrome
60 yo Female with Anxiety

Clinical Notes: RAISED FERRITIN
Cortisol
Cortisol am 581 nmol/L (160 - 650)
VV

Sullivan Nicolaides Pty Ltd. ABN 38 078 202 196. NATA/ACTA Accreditation No 1964
Tests Completed: Immunoassays, CFF, R/LFT, TFF, Cortisol AM, FHE, ESR
Tests Pending: Red Cell Zinc
Sample Pending:

34 yo Female with Bulimia, Anxiety & Severe Depression

Cortisol
Cortisol am 1210 H nmol/L (160-653)


- Some anxious/stressed individuals present with a very similar stressed picture but actually have low-end cortisol
- These patients may also have low serum Na with difficulty maintaining their electrolytes as part of this poor adrenal function
- However, there is increasing research that the HPA issues stem less from low adrenal output and more from an excessively strong negative feedback loop
- Documented prevalence in PTSD and some depression subtypes as well as CFS, Fibromyalgia, Chronic pain, Obesity and AIDS and Cancer Survivors

Copyright Rachel Arthur 2014. All rights reserved. This document is provided to the purchaser for their individual professional use and may not be copied or distributed without the prior written permission of Rachel Arthur.
HPA axis – a reminder!

39 yo Anxious Female with extended history of trauma from a young age

‘Extremely stressed at time of test’
Treatment Approach for High Cortisol Depression

- Use of corrective nutrients
  - Tyrosine
    - To support a healthy stress response via production of NAD
  - Vitamin C supplementation 3g /d sustained release form (Brody et al 2002)
    - Attenuation of increases in SBP, DBP, subjective stress etc.
    - Faster recovery of salivary cortisol after psychological stress
    - No change in amount of cortisol released

Treatment Approach for High Cortisol Depression

- Magnesium
  - RCTs demonstrate reduction in ACTH or nocturnal cortisol levels (Held et al 2002, Murck & Steiger 1998)
  - Attenuation of secondary reduced thyroid hormone activity (Cinar 2007)
- α-Lipoic acid
  - Maintenance of healthy blood glucose handling for extreme high cortisol situations
  - Enhanced elimination of catecholamines (Kelly 1999)
Treatment Approach for High Cortisol Depression

- **Phosphatidylserine**
  - 400-800mg per day shown to enhance mood during mental stress (Hellhammer et al 2004; Starks et al 2008)
  - Blunt ACTH & cortisol release
- **Alkaline/ lactovegetarian diet or administration of sodium or potassium bicarbonate**
  - RCTs demonstrate reduction in plasma & 24hr urinary free cortisol (McCarty 2005; Remer et al 2008)

Treatment Approach for Low Cortisol Depression

- **Herbs:** Licorice & Rehmannia
- **Vitamin B₅**
  - May improve adrenal response to ACTH
  - In all panthenol treated subjects a significant increase in urinary excretion of 17-alpha-21-dihydroxy-20-keto steroids has been observed and it appeared to be higher in male ageing between 18 and 25 (Fidanaza et al 1981)
- **Sodium** – preferably not as NaCl
  - Especially for patients with low blood pressure
- **Vitamin C**
A Case for Oestrogen
(Krishnan & Nestler 2010, Brummelte & Galea 2009, Solomon et al 2009)

- Increased rates of depression in women
- Especially during post-partum and peri-menopausal period
- ‘Oestrogen’ has anti-depressant properties & can augment the action of other monoamines
- Wide distribution of E2 β receptors in the CNS – suggest possible role in BDNF, serotonin signalling, increased DOP release & HPA axis functioning

A Case for Oestrogen
(Krishnan & Nestler 2010, Brummelte & Galea 2009, Solomon et al 2009)

- Current theories suggest that it’s the fluctuations in sex steroid hormones rather than the actual levels that may cause depression
- “Ovarian withdrawal hypothesis”
Treatment Approach for the Low Oestrogen Depressive

- Herbs: False Unicorn Root, Black Cohosh, Shatavari, Korean Ginseng, Maca
- Vitamin E 500IU/d
- Phytoestrogens?

A Case for Progesterone (Casas et al 2011, Li et al 2012)

- Progesterone has multiple positive actions on mood & cognition including neurogenesis, anxiety control & neuroprotection.
- ‘Progesterone withdrawal’ has been significantly implicated in luteal phase mood issues & especially PMDD
- Animal models reveal a drop in Progesterone results in moderate social withdrawal & anhedonia without any changes in 5HT
Treatment Approach for the Low Progesterone Depressive

- Herbs: Vitex agnus-castus, Peonia lactiflora
- Zinc 15-30mg/d
- B6 200mg/day


- Most (but not all) studies have found a correlation between lower free T levels & depressive or dysthymic sx
- Reduced T concentrations may precede and predict the onset of symptoms of depression, a risk factor MDD?
- Additional evidence points to possible influence from AR genotype → possibly explaining why the ‘same’ free T level can produce different clinical pictures in men
So...do depressed men need Testosterone replacement? (Amore et al 2012, Sankar & Hampson 2012, Hintikka et al 2009)

- In a word....No
- Results of studies of T therapy in depressed men very varied
- Amore et al. conclude that it has failed to show sound evidence of efficacy in depression
- Certainly appears to help small % on some parameters:
  - Improved sexual function (independent of mood)
  - Improved muscle strength & cognitive function
- However, contraindications and risks associated

Drivers of Low Androgens In Males

- Obesity
- IR
- CVD
- Smoking
- ↑ CRP
- ↑ Hcy

- Inflammation & Oxidative Stress
- ↑ Prolactin
- ↑ E2 – endo/exo
- ↑ SHBG

- Stress
- Testicular trauma
- Radiation
- Meds

- Trauma & iatrogenic

- Ageing?
Low Androgens - Go back to addressing the cause

- Obesity
- Insulin resistance
- Alcohol & illicit drugs
- Inflammation & oxidative stress
- HPA axis over-activation
- Psychological Stress
- Basic nutritional adequacy esp. ample antioxidants

---

40yo Marked Depression, Demotivation & Poor Memory

<table>
<thead>
<tr>
<th>Androgens</th>
<th>Testosterone</th>
<th>nmol/L</th>
<th>(11.0 - 40.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydro Epiandrosterone Sulphate (DHEAS)</td>
<td>DHEAS</td>
<td>6.2</td>
<td>(2.4 - 11.6)</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Cortisol am</td>
<td>515</td>
<td>(160 - 650)</td>
</tr>
</tbody>
</table>

Comments on Collection 593024383
TREATMENT APPROACHES FOR LOW TESTOSTERONE DEPRESSION

Brain – Impaired Regulation, Altered NTs, Psychosocial
- Address the stress & counselling
- Rhodiola & Tyrosine
- Damiana
- Panax ginseng
- Folate, K2 & Zinc

Testes - Low Androgens
- Zn, Se, Boron
- Vitamin K2
- Tribulus & Damiana

Fat & Inflammatory Lifestyle – Xs E2
- Weight loss & ↓ Alcohol
- Minimise environmental oestrogens & increase phytoestrogens
- Green tea, mushrooms, flavonoids, Damiana & proanthocyanidins, pomegranate
- Turmeric, resveratrol, N-acetyl cysteine, cysteine

Cardiovascular – NO issues
- Folate & methyl donors
- Arginine
- Tribulus, Panax & Damiana
- Pomegranate & broad antioxidants

Copyright Rachel Arthur 2017. All rights reserved. This document is provided to the purchaser for their individual professional use and may not be copied or distributed without the prior written permission of Rachel Arthur.
Tribulus Formula

Supplemental Facts

Amount Per Serving
Three vegetarian capsules contain:
- Tribulus Terrestris .............................................................. 250 mg
  (standardized to contain 20% protodioscin)
- D-aspartic acid ................................................................. 1,000 mg
- L-citrulline ..................................................................... 180 mg
- L-Arginine .................................................................... 50 mg
- Acetyl L-Carnitine ......................................................... 30 mg
- Other ingredients: Hypromellose, plant fiber (cellulose), ascorbyl palmitate, vegetarian capsule (cellulose, water)

Not to be taken by pregnant or lactating women. Consult a health professional before taking this or any other product.

5-8 capsules daily in divided doses, between meals.

Copyright Rachel Arthur 2017. All rights reserved. This document is provided to the purchaser for their individual professional use and may not be copied or distributed without the prior written permission of Rachel Arthur.
Pyrroles & the Theory of Pyroluria

- First discovered in 1950s in the urine of a large proportion of schizophrenic patients by two researchers: Abraham Hoffer & Carl Pfeiffer
- A pyrrole compound: OHHPL (hydroxyhemoppyrrolin-2-one) which is an intermediate metabolite of heam can be found in the blood or CSF of all individuals
- Only found in significant concentrations in the urine of a minority of people → believed to be a biochemical aberration
- Produces a ‘mauve spot’ on paper chromatograms → “Mauve Factor”
Pyrroles - Physiologic & Nutritional Implications

- Increased oxidative stress (cause or consequence?)
- Decreased haem levels → reduced anti-oxidant defence enzymes
- Significantly decreased zinc & vitamin B6 possibly via complexing with OHHPL
- Strong negative correlation between OHHPL & plasma zinc & PLP levels
- Depletion of rbc Arachidonic Acid
- Possible excitatory action of OHHPL

Pyrroluria Signs & Symptoms (McGinnis 2004, Hoffer 1995, Walsh)

<table>
<thead>
<tr>
<th>Poor short term memory</th>
<th>Low stress tolerance</th>
<th>Anxiety/panic/ fear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pale skin</td>
<td>Nausea esp a.m.</td>
<td>Skips breakfast</td>
</tr>
<tr>
<td>Inability to tan</td>
<td>Pessimism</td>
<td>Motion sickness</td>
</tr>
<tr>
<td>Stretch marks</td>
<td>Explosive anger</td>
<td>Social isolation</td>
</tr>
<tr>
<td>Nail white spots</td>
<td>Hyperactivity</td>
<td>Easily fatigued</td>
</tr>
<tr>
<td>Premature grey</td>
<td>Emotional lability</td>
<td>Delayed puberty</td>
</tr>
<tr>
<td>Dry skin</td>
<td>Impulsivity</td>
<td>SSRI responders</td>
</tr>
<tr>
<td>Light-sound-odour</td>
<td>Perceptual disorganization</td>
<td>Poor dream recall</td>
</tr>
</tbody>
</table>
intolerance            |
### Reported Prevalence of Pyroluria (McGinnis 2004, Hoffer 1995, Walsh)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Reported Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down Syndrome</td>
<td>70%</td>
</tr>
<tr>
<td>Schizophrenia (untreated)</td>
<td>≤ 70%</td>
</tr>
<tr>
<td>Schizophrenia (treated)</td>
<td>≈ 50%</td>
</tr>
<tr>
<td>Schizophrenia (resolved)</td>
<td>0%</td>
</tr>
<tr>
<td>Autism</td>
<td>50%</td>
</tr>
<tr>
<td>ADHD</td>
<td>30%</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>≤ 80%</td>
</tr>
<tr>
<td>Depression</td>
<td>≈ 20%</td>
</tr>
<tr>
<td>Violent criminals</td>
<td>?</td>
</tr>
</tbody>
</table>

### Treatment Approaches for the Pyrrole Based Depression

- Assessment via urinary pyrrole assay
- **Combination treatment with high dose Zn, B6 and arachidonic acid plus general antioxidants**
- Doses are proportionate to level of pyrroles seen in urine, bodyweight, digestive efficacy etc.
- **Doses should be increased during periods of stress to meet increased anti-oxidant demand**
INFLAMMATION MODEL

The Inflammation Model

Hypothesis

- Excess inflammatory mediators within the brain disturb both normal cell wall function & interfere with neurotransmitter levels
Depression and Oxidative Stress: Meta-Analysis

Forest plot of effect sizes of associations between depression and oxidative stress


CNS Immune System (Alexopoulos & Morimoto 2012. The inflammation hypothesis in geriatric depression)

- Historically brain considered an immuno-privileged organ
- CNS has own immune system that is distinct from but interacts with peripheral immunity
- CNS immunity regulated primarily by microglial cells
- Microglia exist primarily in dormant/quiescent state
- However they move through several stages of activation which leads them to be central players in CNS inflammation
- This response can be neuroprotective or neurotoxic
A Case for Inflammation

Evidence
- Cytokines injected into rodents induce reproducible depressive behaviour (Krishnan & Nestler 2010)
- Success of the PGE2 inhibitors & mood stabilisers
- Strong epidemiological links with low Omega 3s
- Neurons in depressed patients display inflammatory characteristics
- Rbc's demonstrate increased vulnerability to oxidation
- Depressed blood levels of antioxidants (Garlecki et al 2009)
- Increased activity of SOD, GPx (not all studies) generally seen in these patients
Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways

Michael Maes, Michael Berk, Lisa Goehler, Cai Song, George Anderson, Piotr Gałecki and Brian Leonard

Abstract
It is of considerable translational importance whether depression is a form or a consequence of sickness behavior. Sickness behavior is a behavioral complex induced by infections and immune trauma and mediated by pro-inflammatory cytokines. It is an adaptive response that enhances recovery by conserving energy to combat acute inflammation. There are considerable phenomenological similarities between sickness behavior and depression, for example, behavioral inhibition, anorexia and weight loss, and melancholic (anhedonia), physio-somatic (fatigue, hyperalgesia, malaise), anxiety and neurocognitive symptoms. In clinical depression,

Keywords: depression, sickness behavior, inflammation, oxidative stress, cytokines

Introduction
The first inkling that there are phenomenological similarities between clinical depression and sickness behavior and that both conditions may share common pathways, that is, activation of the inflammatory responses system (IRS) was published in 1993 [1,2]. Sickness behavior is a behavioral complex that is typically induced by acute infections and tissue injury in many mammalian species. The characteristic behavioral pattern consists of malaise, hyperalgesia, pyrexia, listlessness and disinterest in social interactions with the environment, lethargy, behavioral inhibition,

Figure 1 Inflammation causes sickness and depression.

Nutrition & mental well being & behaviour


Fig. 1.
Kynurenine pathway of tryptophan metabolism. IDO, indoleamine 2,3-dioxygenase; KMO, kynurenine-3-monoxygenase.

Nutrition & mental well being & behaviour
Inflammation Model

- What diet & lifestyle choices could produce this effect in an individual?

- Excess omega 6:3
- Inadequate Omega 3
- Low anti-oxidant intake generally
- High oxidative Stress e.g smoking
- Pathogenic dysbiosis
- Neuro-degenerative
- Unresolved chronic infection e.g. bacterial or viral (even something as simple as HSV)
- Other inflammatory conditions e.g CVD, NIDDM, allergies etc

Recognising Inflammatory Depression

Look for the following features:

- Imbalance of oxidants & antioxidants – diet & lifestyle
- Chronic immune problems e.g. CMV, HSV, RRF
- Chronic inflammatory conditions e.g. IBD, CVD, T2DM
- Chronically elevated white cells – might not be all types nor out of reference range (see examples)
- Elevated hsCRP – not always reliable
- Patient’s depression markedly worse when ‘sick’
21yo Male with Depression & Anxiety on Effexor with minimal response to treatment

### Haematology

<table>
<thead>
<tr>
<th>Date</th>
<th>17/02/12</th>
<th>07/06/12</th>
<th>10/07/12</th>
<th>26/10/12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time F-Fast</td>
<td>1755</td>
<td>0710 F</td>
<td>1530</td>
<td></td>
</tr>
<tr>
<td>Lab Id.</td>
<td>586549081</td>
<td>580073594</td>
<td>589219057</td>
<td>590127620</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>150</th>
<th>145</th>
<th>144</th>
<th>140</th>
<th>g/L (135-175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.46</td>
<td>0.46</td>
<td>0.45</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>RCC</td>
<td>4.9</td>
<td>4.8</td>
<td>4.7</td>
<td>4.6</td>
<td>10^12/L (4.5-6.5)</td>
</tr>
<tr>
<td>MCV</td>
<td>93</td>
<td>96</td>
<td>94</td>
<td>94</td>
<td>fL (80-100)</td>
</tr>
<tr>
<td>WCC</td>
<td>6.7</td>
<td>7.5</td>
<td>8.5</td>
<td>6.5</td>
<td>10^9/L (3.5-10.0)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>3.87</td>
<td>4.85</td>
<td>5.74</td>
<td>4.01</td>
<td>10^9/L (1.5-6.5)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.63</td>
<td>1.88</td>
<td>1.42</td>
<td>1.95</td>
<td>10^9/L (1.5-4.5)</td>
</tr>
<tr>
<td>Monocytes</td>
<td>1.02 H</td>
<td>0.60</td>
<td>1.29 H</td>
<td>0.58</td>
<td>10^9/L (0-0.5)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.09</td>
<td>0.11</td>
<td>0.04</td>
<td>0.09</td>
<td>10^9/L (0-0.5)</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.10</td>
<td>0.01</td>
<td>0.01</td>
<td>0.02</td>
<td>10^9/L (0-0.15)</td>
</tr>
<tr>
<td>Platelets</td>
<td>322</td>
<td>306</td>
<td>281</td>
<td>328</td>
<td>10^9/L (150-400)</td>
</tr>
<tr>
<td>ESR</td>
<td>9</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>mm/h (1-12)</td>
</tr>
</tbody>
</table>

---

21yo Male with Depression & Anxiety on Effexor with minimal response to treatment

<table>
<thead>
<tr>
<th>Date</th>
<th>17/02/12</th>
<th>07/06/12</th>
<th>26/10/12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time F-Fast</td>
<td>1755</td>
<td>0710 F</td>
<td>1215</td>
</tr>
<tr>
<td>Lab Id.</td>
<td>586549081</td>
<td>580073594</td>
<td>590127620</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2</th>
<th>&lt;1</th>
<th>&lt;1</th>
<th>mg/L (0-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment Approaches for Inflammatory Depression

- Identifying & addressing the source of the inflammation
- Omega 3s
- N-acetyl-cysteine
- Zinc
- Curcumin & Saffron
- Magnesium
- SAMe

The Case for Omega 3 in Depression

- Readily crosses the BBB
- Represent a therapy that influences both structure (DHA) & function (EPA & inflammation)
- Increase BDNF levels
- Suppresses phosphatidyly-associated transduction pathways
- Blocks calcium ion influx
- Direct inhibition of protein kinase C
- Play an active role in neuronal membrane function, fluidity and control of neuronal growth factors
- May influence noradrenergic and serotonergic neurotransmission and receptor function
The Case for Omega 3 (EPA) in Depression


- The findings of a number of studies show a correlation between low erythrocyte n-3 FAs and suicide attempts, one of these demonstrating an eightfold difference in suicide attempt risk between the lowest and highest RBC EPA level quartiles. (Huan et al 2004)

- Major limitation of studies to date using omega 3 is use of markedly different forms, doses and other key study characteristics, making comparisons and conclusions difficult (Grenyer et al 2007, Sarris et al 2016)

- In spite of this there is a general consensus that omega 3 can be beneficial in depression

- Recent reviews focused on eliminating the confounding issues appear to have reached a consensus regarding the superiority of EPA over docosahexanoic acid (DHA) for depression (Sublette et al 2011)
Clinical application of Omega 3 oils

- Therapeutic doses used in trials: 1-2 g/day EPA
- If using a combination EPA & DHA supplement, ensure >60% EPA and a minimum of 200-2,200 mg EPA in excess of DHA will produce best results (Sublette et al 2011)
- Response Time: 3 wks – 6 wks
- Side effects: mild GIT upset in high doses (approx. 15gm per day) such as nausea, loose stools and “fishy” breath (Stoll et al. 1999).

Cautions and Contraindications:

- Caution in conjunction with anticoagulants (doses of total omega 3 ≥ 10g/day)
- Safety is excellent and as such represents the first oral anti-depressant safe in both pregnancy, lactation and children
- Safe in both depressive and manic states and therefore suitable in both pt with diagnosed bipolar disorder and in those with suggestive history
A Case for N-Acetyl Cysteine (NAC)

- Immediate precursor to GSH
- Key antioxidant and anti-inflammatory agent
- Also shown to enhance brain SOD activity
- Moderates Glutamate → reducing impulsivity, addiction, craving (Berk et al 2009)
- Better absorbed than Cysteine - the extra acetyl group helps to stabilise against oxidation. (Dekhuijzen 2004)

A case for NAC
(Berk, M. Science of Nutrition in Medicine & Healthcare Sydney 2011)

- Glutathione (GSH) is the brain’s principal antioxidant
- Preclinical data shows that NAC raises brain GSH & reverses models of GSH depletion
- NAC reverses animal models of oxidative stress, has anti-inflammatory properties & enhances neurogenesis & neuronal survival & reverses mitochondrial toxicity
- 2 RCTs patients with schizophrenia & bipolar disorder received 2g/d of NAC or placebo as adjunct to medication over 2 months. NAC treated patients showed significant improvement on depression, QOL & functioning

**NAC in Depression** (Berk et al 2014, Carvalho et al 2013, Deepmala et al 2015)

- 2 studies: 1 controlled & 1 uncontrolled (case series)
- Both produced positive results but not on every outcome measured

**Most noteworthy** (Berk et al 2014)

- DBPCT (n= 252) individuals with MDD 12 wks
- Administered 2g/d NAC as adjunct
- Statistically significant improvement in multiple outcomes compared with placebo but MADRS scores, response and remission rates did not become statistically significant until 16 wks
NAC in Depression (Berk et al 2014)

Most noteworthy features of noteworthy study!

- Berk’s data suggests that the greatest clinical improvement seen at 6mo
- Sub-group analyses reveal better efficacy in elderly than young patients
Who Might Benefit from NAC?

- In addition to the **indicators of inflammation** generally
  - Compulsive nail biting
  - Impulsivity, the ‘revved up’ anxious depressive
  - Any depression that worsens with comorbidities (Magalhaes et al 2012)
  - Consider elevated GGT in absence of:
    - Alcohol, paracetamol intake
    - Liver diseases
    - Epstein Barr virus, cytomegalovirus and Reye’s syndrome
    - Pancreatic disease
    - Myocardial infarction

Clinical Application of NAC

- **Therapeutic doses used in trials:** 1-6g grams per day, most typical starting dose of 2g/d
- **Response Time:** < 2mo
- **Side effects:** No significant side effects have been reported. Patient compliance can be compromised by the smell and taste of the product however.
Cautions and Contraindications:

- **Smokers** – past or present?
  - Increased progression of lung tumours in mice fed a diet rich in NAC and Vitamin E
    (Sayin et al. 2014)

- **Patients with peptic ulcers** (Ziment 1988)

- **Patients with Candida infections** (Giordani et al. 2002, Yilmaz & Celik 2003)
**Monoamine Model**  
(Developed in 1950s and the current medical model)

**Hypothesis**
- Individuals have physically low levels of one or more of the monoamines— particularly serotonin but increasingly also noradrenaline, dopamine

**Evidence**
- Based on the evidence that depressed patients frequently exhibit low 5HT in their cerebrospinal fluid (CSF)

---

**Serotonin Pathway**

```
L-Trp  \rightarrow  5-Hydroxytryptophan  \rightarrow  5-HT  \rightarrow  Melatonin

NAD, Fe, folate, Ca, C

FAD, Fe, PLP, folate

NAD  \rightarrow  Picolinate  \rightarrow  Niacin

Niacin
```

Copyright Rachel Arthur 2017. All rights reserved. This document is provided to the purchaser for their individual professional use and may not be copied or distributed without the prior written permission of Rachel Arthur.

Fig. 1. Kynurenine pathway of tryptophan metabolism. IDO, indoleamine 2,3-dioxygenase; KMO, kynurenine-3-monooxygenase.

Monoamine Theory - The Low 5HT Version

- What diet & lifestyle choices could produce this effect in an individual?

- Impaired insulin
- Inadequate Trp
- Co-factor deficiency e.g. B6, Fe, Folate
- Excess competing amino acids e.g. Tyr/Phe
- Secondary damage to serotonergic neurons e.g. XTC abuse
- Inadequate protein
- B3 deficiency
- Trauma & Grief

Copyright Rachel Arthur 2017. All rights reserved. This document is provided to the purchaser for their individual professional use and may not be copied or distributed without the prior written permission of Rachel Arthur.
A Case for 5HTP

- High bioavailability
- Crosses the BBB without competition with other amino acids
- By-passes the rate limiting step in serotonin synthesis
- Direct precursor to serotonin
- Shown to increase levels of serotonin, noradrenaline, melatonin, dopamine & βendorphin (Birdswall 1998, Iovieno et al 2011)

Trials using 5HTP in MDD

- Much of the research conducted 1960-70s
- Over 30 studies have investigated the use of 5HTP as either a stand-alone or adjunctive treatment
Clinical applications of 5HTP (Iovieno et al 2011)

- Therapeutic doses used in trials & clinic:
  Trials vary between 200mg-3000mg
  Clinically most common dose is 200-300mg in divided doses
- Response time: 3d-2wks
- Side effects: Nausea & stomach upsets in only 8% patients reported. Headaches, insomnia, palpitations. Can produce vivid dreaming if taken too close to bedtime.
- 5HTP related Serotonin syndrome has not been reported but remains a theoretical possibility at very doses much higher than used in humans (Iovieno et al 2011)

Other Serotonergic Agents

- High dose B3
- Herbs: St. John’s Wort & Rhodiola
Linking Molecules to Mood: New Insight Into the Biology of Depression

Vaishnav Krishnan, M.D., Ph.D.
Eric J. Nestler, M.D., Ph.D.

Major depressive disorder is a heritable psychiatric syndrome that appears to be associated with subtle cellular and molecular alterations in a complex neural network. The affected brain regions display dynamic neuroplastic adaptations to endocrine and immunologic stimuli arising from within and outside the CNS. Depression’s clinical and etiological heterogeneity adds a third level of complexity. Pharmacological antidepressants improve depression through complex mechanisms incompletely understood. This review summarizes knowledge of the neural basis of depression and highlights lessons from animal models and human clinical studies and mentions from animal models.

Linking Molecules to Mood
(Krishnan & Nestler American Journal of Psychiatry 2010)

- “After decades of focus on the monoamine theory of depression there is little to confirm that there are actual deficits in either 5HT, NAD or DOP”
- Drugs that increase monoamine levels can produce benefits in approx. 50% of depressed individuals and remission in approx. 30%.
- This tells us that either depression is heterogeneous and/or that we are treating a symptom & are yet to understand the cause
WHAT ABOUT OTHER NEUROTRANSMITTER PROMOTING APPROACHES?

Catecholamine Pathway

Phenylalanine

Tyrosine → L-Dopa → Dopamine → Noradrenaline → Adrenaline

Melanin

Enkephalins

NAD, Fe, folate, C

NAD, Fe, folate

PLP

Cu, C

B₃₁₂, folate

Thyroid Hormones
Low Catecholamines (DOP, NAD) Model

- What diet & lifestyle choices could produce this effect in an individual?

- Inadequate Tyr or Phe
- Excess competing aminos e.g. BCAAs
- High prolonged stress → Tyr depletion
- Neuro-degenerative
- Damage to neurons 2ry to recreational drug use e.g. methamphetamines
- Deficiency of co-factors e.g. Fe, B3, B6
- Genetic polymorphisms e.g. RDS
- Inadequate Protein
- Deficiency of co-factors e.g. Fe, B3, B6

Treatment Approaches to Low Catecholamine Depression

- Ensure iron adequacy
- Herbs: Rhodiola & Vitex agnus-castus
- Tyrosine (up to 100mg/kg) & Phenylalanine (up to 14gd)
- Theanine

- Increases dopamine release via NMDA stimulation
- Decreases CNS serotonin levels overall however increases serotonin levels specifically in the striatum, hippocampus and hypothalamus of rats
- Inhibits glutamate reuptake as a natural glutamate analogue
- Increases GABA concentrations
- Exhibits neuroprotective effects via blocking NDMA receptors
- Can be a useful sleep aid for some patients as well

Preclinical & animal studies have demonstrated marked anxiolytic effects as well as improved mood and cognition

Human studies to date have been limited by the study design with one-off doses of 200-250mg typically administered prior to a stressor

Results suggest attenuated stress response with decreased rises in SBP, HR and salivary cortisol

In reality, repeat chronic dosing may produce more powerful effects in patients
Clinical applications of Theanine

- Therapeutic doses used in trials & clinic:
  Trials vary between 200mg-250mg
  Clinically most common dose is 200-300mg
- Response time: acute response within 30mins
- Side effects: no reported side effects in either animal or human studies investigating theanine (Nathan et al 2006) although headache was reported more frequently 90mins post-dose in one study (Haskell et al 2008)
A Growing List of Potential Toxins?

- Heavy Metals Hg, Pb, Cd, As etc.
- Pesticides and other agricultural contaminants
- Endocrine disrupting chemicals (EDCs)
  - Sex hormone disruption
  - HPT interference
- CNS chronic infections
- And so on and so forth!

A Case for Heavy Metal Toxicity

- Multiple theoretical & documented mechanisms
  - Mitochondrial toxins
  - Source of significant oxidative stress
  - Targeted deposition in the CNS esp. Hg
  - Depletion of key minerals necessary for neuro health e.g. Zn
  - Endocrine disruption e.g. 2ry or 3ry hypothyroidism
  - Impaired detoxification of other toxins
- Limited studies investigating presence of HM toxicity in depressed pt but preliminary studies have found an association with Hg (Kern et al 2014) & Cd & Pb (Stanley & Wakwe 2002)
Treatment Approaches for Heavy Metal Induced Depression

- Identify & if possible quantify magnitude of exposure and toxicity
- Minimise ongoing exposure
- Treat individual with high doses of antagonistic minerals e.g. Ca for Pb, Zn for Cd, Se & Zn for Hg, Si(OSA) & B for Al in the form of modified citrus pectin. Consider additional chelation support e.g. NAC, resveratrol etc.
- Consider actual chelation therapy (either oral DMSA or herbal e.g. Cilantro tincture) in cases of very high toxicity after comprehensive assessment.

Summary

- Research & clinical experience demonstrates the failure of a 'one-size fits all' model of depression in the form of the monoamine theory
- In future sub-types of depression may be identified with differing pathophysiology
- Alternatively a depressed patient can have a mix of several depressogenic drivers at play
- Optimal care of depressed patients requires
  i. Taking a holistic perspective on the whole case and first asking ourselves, 'what else could it be?'
  ii. Identifying and redressing the relevant drivers via CP, pathology results
  iii. Refining the approach and understanding based on treatment responses