

Metabolic agents in psychiatric disorder

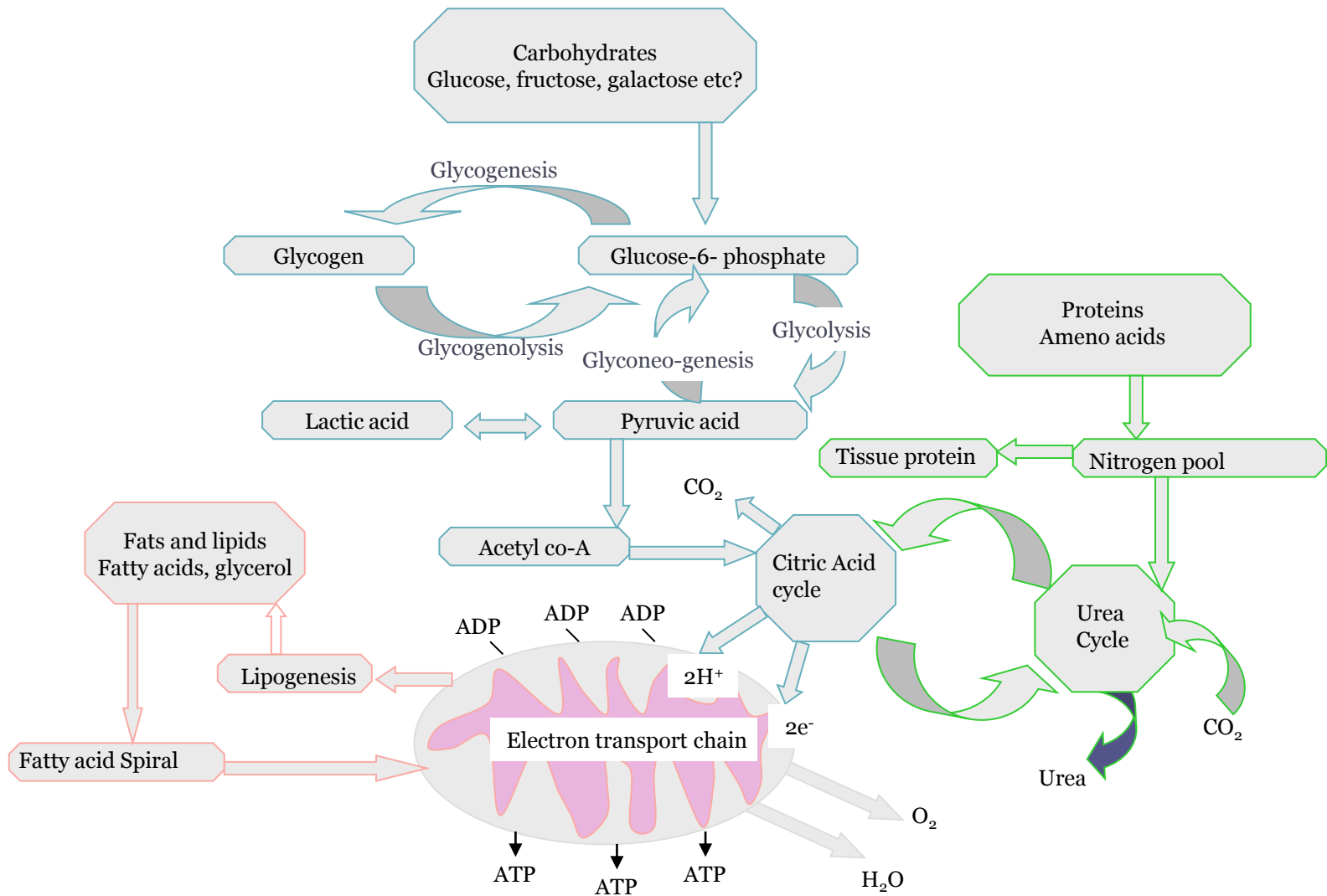
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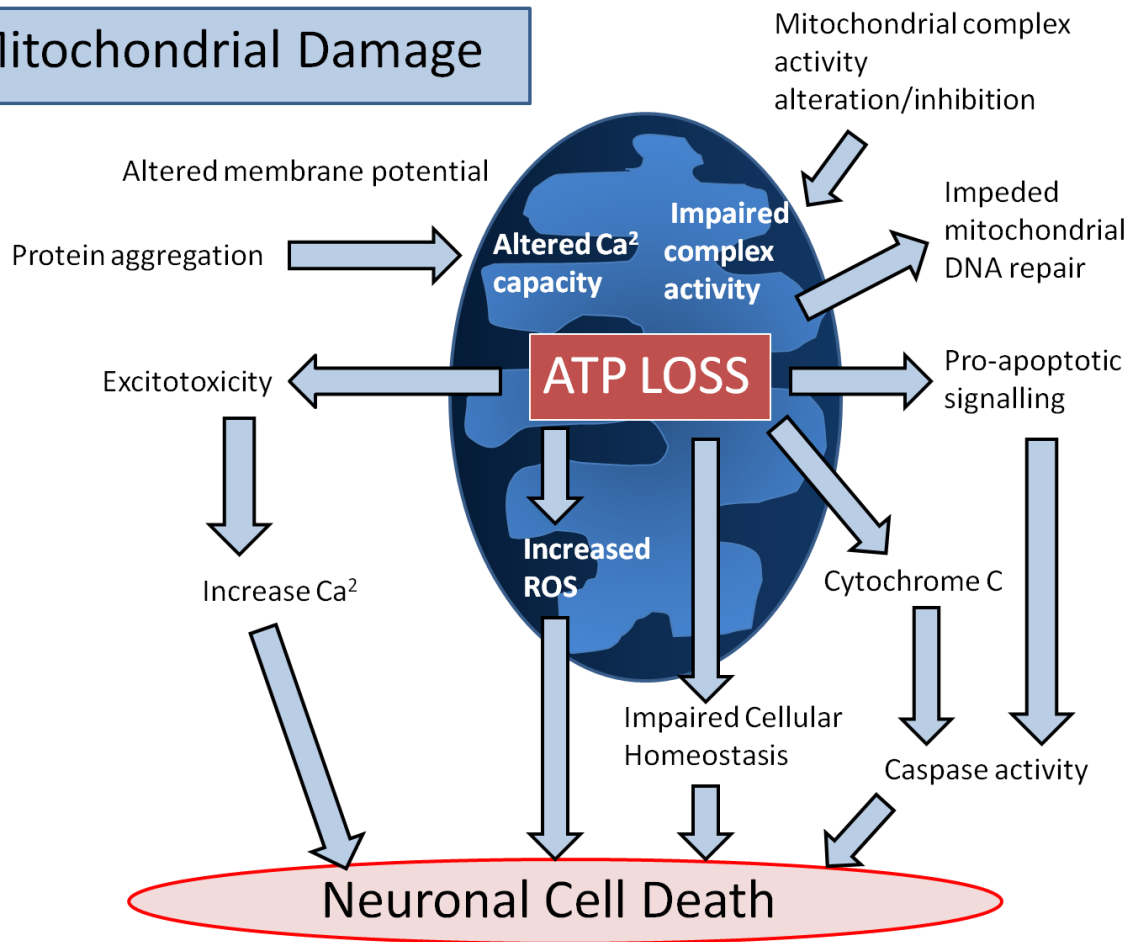
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Energy metabolism

- My background
- Energy metabolism and mitochondria
- Is metabolism different in psychiatric disorders?
- Is there evidence for increase prevalence of metabolic syndrome and mitochondrial disorder in psychiatric populations?
- Nutraceuticals agents for energy production
- Future research- multi centre trial.



Mitochondrial Damage



Is metabolism different in psychiatric disorders?

- In 1932 exercise was found to cause excessive rises in blood lactate levels in schizophrenics. In 1952 a disturbance of energy –regulating mechanisms responsible for the lack of ‘psychic energy’ in schitzophrenics was proposed (Easterday, 1952)
- An involvement of oxidative metabolism was reported by Takajhashi in 1954 and a paradoxical fall in ATP turnover in stressed blood cells not observed in controls was reported in chronic schitzophrenia (Gottlieb 1959)
- reports of impaired glucose regulation prior to the introduction of antipsychotic medications, (Braceland et al 1945) and later, in unmedicated patients,(Schimmelbusch, 1971) patients treated with typical neuroleptic medications (Mukherjee 1989) and patients treated with newer antipsychotics (Newcomer 2002).
- recent reports of elevated levels of diabetes in schizophrenia, compared with the general population (eg, Mukherjee et al, 1989 Subramaniam et al 2003), and impaired glucose regulation during first-episode psychosis in drug-naïve patients Ryan (2003)
- Recent evidence of genetic linkage between 3 regulatory enzymes involved in glycolysis and schizophrenia (Stone 2004)

Is metabolism different in psychiatric disorders

- Changes in brain energy levels and markers of energy metabolism are altered in depression and BD, e.g resting energy expenditure and VO₂ max of individuals during the manic phase were increased compared to controls and euthymic participants (Caliyurt, 2009).
- SPECT data shows blood flow is increased in mania and decreased in depression (Baxter et al 1985). Increased phosphomonoester and decreased adenosine triphosphate (ATP) and phosphocreatine (PCr; a high energy phosphate) in unmedicated depressed.
- Kato et al. 1992. frontal lobe PCr metabolite levels are decreased in patients with severe depression. Subsequent studies suggested that such findings were also seen in patients with bipolar depression in the left frontal region, especially in those with bipolar II disorder and correlated with HAM-D ratings of depression (Kato et al, 1994, 95)

Metabolic syndrome in Psychiatric

- And a far higher incidence of metabolic syndrome in psychiatric patients than non psychiatric (e.g Teixeira & Rocha, 2007)
- 170 patients psychiatric ward
- Higher in women compared to men (43.6% vs 20.8%).
- 48.1% depression
- 38.3% BD
- 31.8 schizophrenia and schitzoaffective disorder
- 5.1% alcoholism
- 23.1% other mental disorders

Mitochondrial diseases

Another recent observation linking metabolic disturbance to psychiatric illness is that the prevalence of psychiatric disorder is far higher in people with mitochondrial diseases.

The first patient with mito disorder was described in 1962 (concept primarily used for defects in respiratory chain) . The first DNA (mtDNA) mutations were described in 1988.

Ubiquitous requirement of energy and unique aspects of mtDNA means that mutations cause huge spectrum of clinical manifestations.

Table 1. Short Summary of Mitochondrial Disorders with mtDNA Mutations

Syndrome	Abbr.	Symptomatology	Psychiatric symptoms	Mutation	Ref.
Presumed primary deletions and rearrangements of mtDNA					
Kearns Sayre Syndrome	KSS	onset before age 20, ophthalmoplegia, ptosis, myopathy, heart block	a case with chronic depression and later visual hallucinations	mtDNA deletions in many tissues	[8-10, 17]
Deletions of the mtDNA secondary to nDNA mutations					
Chronic Progressive External Ophthalmoplegia	CPEO	ophthalmoplegia, ptosis, mild proximal myopathy	cases of depression and bipolar disorder	nDNA genes, mtDNA deletions	[12,18-21]
Mitochondrial NeuroGastroIntestinal Encephalomyopathy	MNGIE	ophthalmoplegia, gastro-intestinal dysmotility, deafness, neuropathy, myopathy, encephalopathy		nDNA gene, (thymidine phosphorylase), with secondary mtDNA deletions and depletion	[13]
Point mutations in the mtDNA					
Chronic Progressive External Ophthalmoplegia	CPEO	ophthalmoplegia, ptosis, mild proximal myopathy		mtDNA 5698	[22]
Mitochondrial myopathy, Encephalopathy, Lactic Acidosis and Stroke-like episodes	MELAS	myopathy, migraine and other cerebral symptoms, diabetes mellitus	cases of hallucinations, major depression, anxiety, schizophrenia, personality change	mtDNA 3243	[23-34]
Leber Hereditary Optic Neuropathy	LHON	visual loss, spontaneous recovery can occur	depression	mtDNA 11778	[7,35]
Myoclonus Epilepsy with Ragged Red Fibres	MERRF	myoclonic and tonic-clonic seizures, ataxia, myopathy, dementia		mtDNA 8344	[36]
Maternally Inherited Leigh's syndrome	MILS	infantile onset subacute encephalopathy		mtDNA 8993	[37]
Neurogenic weakness with Ataxia and Retinitis Pigmentosa	NARP	late childhood or adult-onset neuropathy, ataxia, pigmentary retinopathy		mtDNA 8993	[37]

Abbr.: syndrome abbreviation. Ref.: reference. Several mtDNA mutations have been identified in MELAS, LHON, and MERRF, and there may be considerable overlap between syndromes.

Summary of Non-Medication-Related Mitochondrial Alterations in Bipolar Disorder

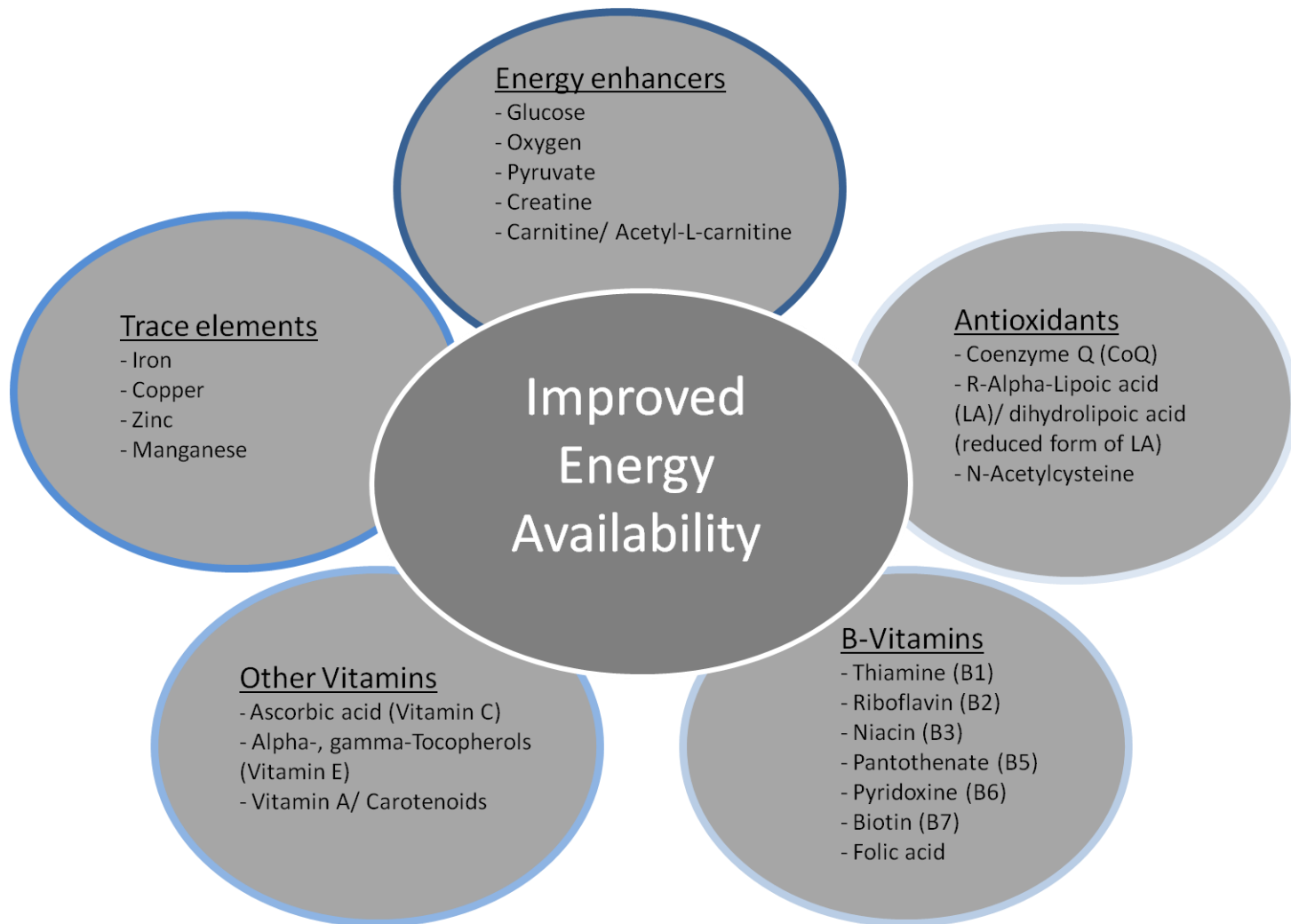
Study	Patients	Controls	Tissue	Analysis	Result (**significant diff, *tendency)
1996 [100]	35	29	leukocytes	mtDNA 5 kb deletion	found in more patients vs. controls *
1997 [102]	7	9	brain	mtDNA 5 kb deletion	increased ratio in patients vs. controls **
2000 [105]	125	184	leukocytes	mtDNA variant at nt 5178 in complex I	found in more patients vs. controls **
2001 [108]	133	171	leukocytes	mtDNA variant at nt 10398 in complex I	found in more patients vs. controls **
2003 [110]	32	11	lymphoblastoid cells	nDNA subunit of complex I expression	decreased in patients vs. controls **
2004 [114]	630	734	leukocytes	mtDNA variant at nt 3644 in complex I	found in more patients vs. controls **
2005 [98]	4	34	brain	mitochondria-related genes	subset up-regulation vs. controls *

Summary of Non-Neuroleptic-Related Mitochondrial Alterations in Schizophrenia

Study	Patients	Controls	Tissue	Analysis	Result (**significant diff, *tendency)
1999 [86]	25	24	platelets	complex I activity	increased in patients vs. controls **
1999 [92]	3	4	brain	mitochondrial profiles	reduction in patients vs. controls *
2002 [95]	6	10	muscle	enzyme ratio and ATP production	decreases in patients vs. controls **
2003 [81]	181	184	lymphocytes	mtDNA variant at nt 12027 in complex I	found in more patients vs. controls **
	15	9	brain		

- There appears to be obvious energy metabolism deficits in certain psychiatric disorders.
- *“The ‘mitochondrial psychiatry’ model proposes that relatively low levels of mitochondrial function, perhaps even on the lower end of the so called ‘normal’ range act in a manner to predispose towards the development of certain psychiatric disorders, and that the effect of pharmacological agents, at least in part, may be due to the effects on mitochondrial function” (Gardner et al 2005)*
- One potential hypothesis is that agents with the capacity to improve mitochondrial function might this be effective in reducing symptomologies in these individuals.

Nutraceutical agents with the capacity to improve energy availability



- **Ubiquinone (coenzyme Q10)** is an endogenous constituent that links mitochondrial complex I and III, transferring electrons between the units. In (MELAS) shown reduction in serum lactate and pyruvate and improvement in brain ATP synthesis and symptomologies at a dosage of 150mg/day.
- **N-acetyl cysteine (NAC)** was recently shown to rescue cognitive deficits caused by mitochondrial dysfunction in transgenic mice tested using a Morris water maze (Otte et al 2011). Recently efficacy of NAC in both schizophrenia and BD In the 6-month BD trial (n=75), adjunctive NAC led to large symptom and quality of life (Berk et al 2008).
- **Acetyl-L-carnitine (ALC)** fatty acids transfer across the mitochondrial membrane. ALC can correct free radical-induced oxidative damage (Silva-Adaya et al, 2008). ATP and phosphocreatine normalized in depressed following ALC treatment. The increase correlated with improvements in symptoms based on HAM-D scores (Pettegrew 2002). Also efficacy in glucose disposal, storage and glucose uptake in metabolically impaired and in normal healthy adults (Mingrone,1999).
- **Alpha lipoic acid** is a key factor in mitochondrial energy generation, appears to reverse oxidative stress secondary to mitochondrial DNA (mtDNA) 4834bp deletion patients with dysthymia, where ALC was equivalent to amisulpride (Zanardi et al 2006),

- **Ascorbic acid** has possible efficacy in mitochondrial myopathy (Eleff et al 1984),, and has a theoretical mechanism of action as an antidepressant in BD through the suppression of vanadium, which is elevated during manic episodes . Ascorbic acid (vitamin C) is also a mediator in L-carnitine production (Arrigoni 2002).
- **Tocopherol (vitamin E)** scavenges free radicals and reduces lipid peroxidation, improving mitochondrial membrane integrity. Studies have suggested that tocopherol and ubiquinone are more efficient when used together (Kagan et al 1990)
- **B vitamins;** many actions but mainly involved in mitochondrial respiration, electron transfer and one carbon transfer pathways, antioxidant status,. Have shown synergistic effects when administered conjunctively with other mitochondrial agents (e.g Dhitavat et al 2005)

Formulation

In this study we will trial the efficacy and tolerability of twice daily dosing of a

- N-acetylcysteine (NAC) 1000mg;
- Acetyl L-carnitine (ALC) 1000mg;
- Ubiquinone (Co Q10) 300 mg;
- Alpha lipoic acid 300mg,
- a-tocopherol (natural vitamin E) 200IU
- ascorbate (vitamin C) 400mg
- thiamin (100mg),
- riboflavin (100mg)
- niacin (400mg),
- pantothenic acid (100mg),
- pyridoxine (100mg)
- folic acid (400 μ g)
- cobalamin (5 μ g),

Method

Participants

- 150 patients meeting DSM-IV-TR criteria for BD (bipolar I, bipolar II and NOS) on a structured clinical interview (MINI-plus) and MADRS > 18 with a current acute depressive episode.

Design

- 12-week, multi-site, randomized, double blind, parallel group trial of a combination therapy (CT) or placebo
- Participants will receive 12 weeks of daily treatment, adjunctive TAU, with assessment visits at baseline, weeks 1, 2, 4, 6, 8, 12 and (washout) 16 weeks.

Trial sites

- Barwon Health, Geelong, the Massachusetts General Hospital, Boston, the Mental Health Research Institute, Melbourne and the CADE Clinic at Royal North Shore Hospital, Sydney.

Outcome measures

Clinical outcomes;

- MADRS, Hamilton Anxiety Rating Scale, Bipolar, Depression Rating Scale, Young Mania Rating Scale, CGI –Improvement and CGI-Severity scales, Patient Global Impression-Improvement subscale, GAF, LIFE RIFT, Q-Les-Q.

Demographic and other

- Age, weight, height, sex, psychiatric history and duration of illness.
- Information on substance use, food frequency questionnaire, physical activity questionnaire.

Blood samples

- Obtained at baseline and at week 12. Analysed for;
- Pyruvate, lactate, blood glucose, oxidative markers such lipid peroxidation products (e.g TBARS, MDA) and oxidative enzymes.

- Different approach to typical Pharmaceutical approach of 'one target' 'one action'.
- Problem of discerning which active will be effective but important to remember that these are food derived products. The human body designed to ingest largest variety of foods compared to all other creatures.
- To date over 150 different pathological point mutations and a similar number of rearrangements (partial deletions and duplications) of mtDNA have been associated with disease. No one single test that will prove or disprove whether a patient has a mitochondrial disorder (Chinnery et al, 2003)
- If psychiatric disorders are a product of mitochondrial dysfunction a multiple target treatment is most likely the most efficacious.