

# Should Depressive Syndromes Be Reclassified as “Metabolic Syndrome Type II”?

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**Background.** A nascent explanatory theory regarding the pathophysiology of major depressive disorder posits that alterations in metabolic networks (e.g., insulin and glucocorticoid signaling) mediate allostasis.

**Method.** We conducted a PubMed search of all English-language articles published between January 1966 and September 2006. The search terms were: neurobiology, cognition, neuroprotection, inflammation, oxidative stress, glucocorticoids, metabolic syndrome, diabetes mellitus, insulin, and antidiabetic agents, cross-referenced with the individual names of DSM-III-R/IV-TR-defined mood disorders. The search was augmented with a manual review of article reference lists; articles selected for review were determined by author consensus.

**Results.** Disturbances in metabolic networks: e.g., insulin-glucose homeostasis, immuno-inflammatory processes, adipokine synthesis and secretion, intra-cellular signaling cascades, and mitochondrial respiration are implicated in the pathophysiology, brain volumetric changes, symptomatic expression (e.g., neurocognitive decline), and medical comorbidity in depressive disorders. The central nervous system, like the pancreas, is a critical modulator of the metabolic milieu and is endangered by chronic abnormalities in metabolic processes. We propose the notion of “metabolic syndrome type II” as a neuropsychiatric syndrome in which alterations in metabolic networks are a defining pathophysiological component.

**Conclusion.** A comprehensive management approach for depressive disorders should routinely include opportunistic screening and primary prevention strategies targeting metabolically mediated comorbidity (e.g., cardiovascular disease). Innovative treatments for mood disorders, which primarily target aberrant metabolic networks, may constitute potentially novel, and disease-modifying, treatment avenues.

**Keywords** Major depressive disorder, Bipolar disorder, Diabetes mellitus, Pathophysiology, Metabolic syndrome

## INTRODUCTION

Mood disorders are highly prevalent syndromes associated with a high rate of non-recovery, recurrence, and inter-episodic dysfunction (1,2). Despite intensified efforts to characterize and uncover pathoetiological factors subserving the “surface-based” phenomena of mood disorders, a clear, comprehensive, and coherent disease model in affective disorders does not currently exist (3). Nonetheless, alterations in neuronal plasticity, cellular resilience, and cytoarchitecture, along with associated regional abnormalities in neuronal (and glial) density and morphology are reported (4). The rationale for scrutinizing the metabolic system as a potential explanatory factor in mood disorders, and a platform for novel drug discovery, is supported by several lines of research (5).

Firstly, a concatenation of findings indicates that major depressive disorder (MDD) is an independent risk factor for new-onset type II diabetes mellitus (DM) (6). Secondly, MDD is associated with significant alterations in disparate physiological processes (e.g., decreased insulin sensitivity, immuno-inflammatory activation), which presage the depressed individual's vulnerability to type II DM (7). Thirdly, neuroimaging studies (e.g., positron emission tomography; PET, functional magnetic resonance imaging; fMRI) have persuasively reported regional alterations in brain metabolic activity at rest and following emotional/cognitive provocation (8). Also, similar to diabetic populations, the single largest cause of premature mortality in persons with mood disorders relates to abnormal insulin sensitivity (i.e., cardiovascular disease) (9,10). This latter observation has important implications for patient management and public-health initiatives (11).

Herein, we propose that MDD could be conceptualized as a “metabolic disorder” (i.e., “metabolic syndrome type II”), in which alterations in metabolic networks are a salient pathophysiological component and potential target for novel, potentially disease-modifying treatments. Towards this aim, we highlight the reciprocal relationship between MDD and DM with respect to neuroimaging abnormalities, neurocognitive deficits, and potential mediators linking these syndromes.

## METHODS

We conducted a PubMed search of all English-language articles published between January 1966 and September 2006. The search terms were: neurobiology, cognition, neuroprotection, inflammation, oxidative stress, glucocorticoids, metabolic syndrome, DM, insulin, and anti-diabetic agents, cross-referenced with the individual names of DSM-III-R/IV/-TR-defined mood disorders (e.g., major depressive disorder, bipolar disorder). The search was augmented with a manual review of article reference lists; articles selected for review were determined by author consensus.

## *Mood Disorders and Diabetes Mellitus: The Clinical Overlap*

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion and/or insulin action (12). Like MDD, DM is highly prevalent affecting approximately 8% of the adult population with higher rates in older individuals. Several racial and ethnic groups are at a particularly high risk (e.g., African Americans, Hispanics, and Asians) and DM is associated with substantial illness-related morbidity and mortality (7).

Extant data indicate that the prevalence of glucose handling disturbances in the mood disorder population may be several-fold greater than the age-adjusted mean in the general population (13–15). Original reports, which first appeared in pre-DSM and pre-psychopharmacological eras chronicled higher rates of abnormal glucose tolerance, insulin resistance, and syndromal DM among psychiatric probands and their unaffected first-degree relatives (16–18). Due to methodological insufficiencies, these original investigations did not permit definitive conclusions regarding the hazard rate for DM in mood disorders.

Results from more recent investigations indicate that both cross-sectional and longitudinal associations exist between mood disorders and DM (6,19,20). Taken together, the prevalence of DM is increased by approximately two-fold amongst persons with mood disorders and vice versa. Moreover, MDD is potentially an independent risk factor for insulin resistance and associated syndromes (e.g., Alzheimer's disease) (21–23). The link between insulin resistance and Alzheimer's disease may be mediated by the metalloprotease enzyme insulin-degrading enzyme (IDE) which catabolizes  $\beta$ -Amyloid and insulin (24,25). Although the association between MDD and DM is reasonably well established, the direction of this relationship is unknown and the possibility that confounders (e.g., antidepressant treatment) alone and/or in combination may parsimoniously explain the link has not been excluded.

## *Mood Disorders and Diabetes Mellitus: Disorders of the Brain?*

An explanatory theory regarding mood disorder pathophysiology posits that depressive syndromes are possibly neurotoxic (26–30). For example, postmortem and preclinical studies have documented abnormalities in cellular plasticity, cellular resilience, and intracellular signaling. Regional and layer-specific alterations in the size, shape, and density of neurons and glia are also documented (4).

Neuroimaging investigations have also identified regional abnormalities in brain structure and function correlating with depressive episode frequency and illness duration; suggesting a neurobiological progression of illness (31–33). For example, bilateral hippocampal volume reduction is a consistently reported abnormality in samples of multiple-episode/chronic

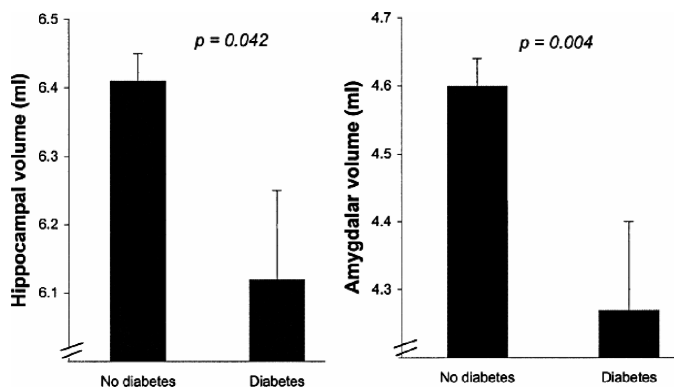
patients (31,32). Abnormalities in other regions-of-interest (ROI) (e.g., amygdala) have also been variably reported (8,34).

Interestingly, regional volumetric abnormalities preliminarily reported in diabetic samples are similar to findings in depressed patients. For example, Den Heijer et al. investigated the association between type II DM, insulin resistance, and the degree of hippocampal and amygdalar atrophy in non-demented subjects ( $n=563$ ; ages 60–90 years) (35) (Figure 1). Diabetic subjects had smaller bilateral hippocampal and amygdalar volumes, which remained significant after accounting for markers of vascular disease (35).

Convit et al. reported that non-diabetic, non-demented, subjects ( $n=30$ ; mean age: 69) with abnormal glucose tolerance exhibited smaller hippocampal volumes along with an associated decrease in memory (i.e., immediate and delayed) performance. Delayed paragraph recall was also significantly correlated with hippocampal volume. No further brain volumetric abnormalities were noted in other brain ROIs (e.g., parahippocampal gyrus, the superior temporal gyrus) (36).

Extending these results further, Musen et al. evaluated the effect of type I DM on gray matter density by comparing diabetic individuals ( $n=82$ ) to an age-matched healthy control group. Gray matter volumes were measured with voxel-based-morphometry (VBM) analysis of magnetic resonance imaging (MRI) data. Gray matter decrements in the left and right superior temporal gyri (STG), left angular gyrus, left middle temporal and middle frontal gyri, and left thalamus were reported in subjects with type I DM compared to the controls. Furthermore, the presence of type I DM remained a significant predictor of gray matter STG density loss after controlling for diabetes status, age, sex, handedness, education, depression, drug and alcohol use (37).

Neurocognitive deficits, a surrogate of diminished brain function, are well documented in depressed and diabetic clinical samples. For example, euthymic individuals with MDD and diabetic patients manifest deficits in measures of sustained attention, working memory, and executive function (38,39). The abnormalities reported in MDD populations are independent of psychopharmacological treatment (40,41).



**Figure 1** Hippocampal volumes and amygdalar volumes (+standard error) on brain MRI in participants with diabetes ( $n = 41$ ) and without diabetes ( $n = 465$ ). Volumes are adjusted for age and sex and normalised to average head size. Reprinted with permission from (35).

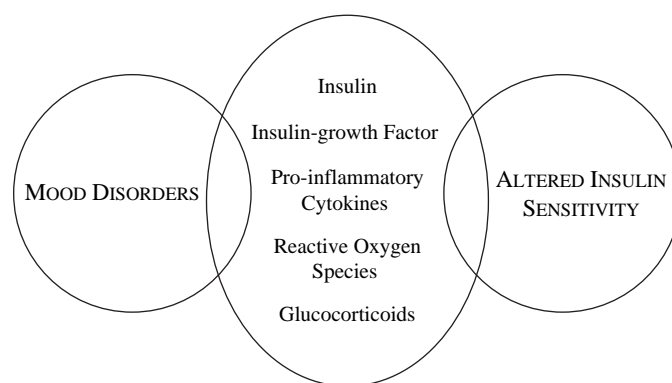
Moreover, MDD individuals with a more severe illness, as indicated by greater lifetime duration of illness, higher frequency of prior episodes, psychotic symptoms, symptom chronicity, and number of hospitalizations, may have more pronounced neurocognitive deficits (42). Collectively, these data suggest that the degree of neurocognitive impairment may be a progressive phenomenon; a rival hypothesis is that they constitute a prodrome to a more pernicious disease.

Optimal neuronal function relies on a continuous supply of glucose as an energy substrate (43). Alterations in glucose availability and utilization would be predicted to adversely affect brain function. Consequently, it is not surprising that neurocognitive deficits have been documented in diabetic populations for decades (i.e., diabetic encephalopathy) (44). Neurocognitive performance abnormalities have been reported across multiple domains including: non-verbal and verbal intelligence, information processing, visuospatial ability, attention, executive function, learning, and memory (35,45,46).

Taken together, results from neuroimaging and neuropsychological investigations in depressive and diabetic populations indicate that both conditions are associated with abnormalities in brain morphology and function. Putative mediating variables common to both conditions are alterations in insulin-glucose homeostasis, immuno-inflammatory processes, and oxidative stress mechanisms (47–50).

### ***Insulin and Insulin Growth Factor: Central Nervous System Modulators (Figure 2)***

The localization of insulin (and its receptors), in brain regions subserving cognitive and emotional function underscores its putative relevance to the pathophysiology and treatment of psychiatric disorders. For example, brain insulin receptors ( $\text{InsR}_b$ ) are regionally distributed throughout the CNS co-localizing with specific isoforms of the facilitative glucose transporter. In the murine brain, the highest  $\text{InsR}_b$  (and mRNA) densities are localized to the hippocampus, olfactory bulb, amygdala, septum, hypothalamus and cerebral cortex (2; 7–9).



**Figure 2** Mood disorders and impaired insulin sensitivity: overlapping pathophysiology.

Collectively, these regions form neural networks that putatively subserve neurocognitive function and affect regulation.

Insulin is delivered to the CNS across the blood-brain barrier (BBB) via a saturable-insulin receptor-mediated transport process. Acute systemic hyperinsulinemia is associated with an increase in cerebral spinal fluid (CSF) insulin concentration; conversely, chronic hyperinsulinemia is associated with a decrease in CSF insulin concentration (via down-regulation of BBB insulin receptors) (43). These observations form the basis for hypothesizing that medical disorders characterized by altered insulin sensitivity and/or chronic hyperinsulinemia (e.g., DM, mood disorders) are de facto brain insulinopenic states (43).

It is increasingly recognized that neuronal insulin is a critical peptide subserving a host of important CNS processes relevant to normal and abnormal function. For example, insulin inhibits the firing of neurons in the hippocampus and hypothalamus; inhibits the reuptake of norepinephrine in rat brains; modulates catecholamine turnover in the hypothalamus, stimulates phosphoinositol turnover in the hippocampus; and regulates norepinephrine and dopamine transporter mRNA concentration in neurons (43,51–54). Insulin can also be categorized as a neurotrophic peptide promoting neuronal growth and synaptogenesis (43).

The role of insulin in neurocognitive function, particularly memory and learning, is compelling. For example, diabetic rats (i.e., streptozotocin-treated) manifest abnormalities in classical and operant conditioning (43,55–57). Moreover, individuals with Alzheimer’s disease manifest higher rates of DM type II, impaired glucose tolerance and high insulin concentrations (43,58–62). The salience of insulin disturbances to the pathophysiology of Alzheimer’s disease has provided the basis for the nosology of “type III diabetes” (63). Long-term potentiation (LTP), a biological model of memory and learning, is principally mediated by glutamatergic signaling (i.e., N-methyl-D-aspartate: NMDA). Insulin modulates intracellular signaling cascades salient to LTP physiology (64).

Over the past decade, there has been increasing interest in the effects of insulin-related growth factors on CNS integrity and function. For example, insulin-like growth factor-1 (IGF-1), structurally related to pro-insulin, is synthesized primarily in the liver and possibly other tissues after priming by growth hormone (65). Liver-derived circulating IGF-1 traverses the BBB, binding to IGF-1 receptors which are regionally distributed throughout the olfactory bulb, amygdala, thalamic nuclei, and hippocampus (66). Insulin-like growth factor-1 is involved in the normal development of mammalian brain tissue and is an important mediator of neurogenesis, synaptogenesis, anti-apoptosis and neuroprotection. Preliminary studies suggest that peripheral IGF-1 levels are correlated with cognitive abilities in older subjects (67–69).

Taken together, insulin and its related growth factors (e.g., IGF-1) are neuropeptides involved in a host of critical CNS functions. Alterations in peripheral insulin-glucose homeostasis differentially affect metabolically demanding organs (e.g., brain). The pernicious effects of MDD and DM on

cardiovascular function are well established (9). The neurotoxic effects of MDD on brain structure and function are indicated by extant data. Preliminary results also indicate that DM may be associated with significant, possibly progressive, abnormalities in CNS integrity.

**Major Depression and Diabetes Mellitus:  
Shared Pathophysiology**

*Inflammatory Systems*

Pro-inflammatory activation refers to the synthesis, secretion, and action of pro-inflammatory cytokines, chemokines, acute-phase reactants, and cellular adhesion molecules (Table 1). For example, increased serum and/or plasma concentration of interleukin-6 (IL-6), and C-reactive protein have been frequently reported in depressed samples and are significantly correlated with depressive symptoms severity. Activated pro-inflammatory cytokines induce “sickness behavior”; a syndrome phenotypically similar to depressive disorders which includes anorexia, sleep disturbance, and decrease in self-care behavior (70).

Cellular adhesion molecules include soluble intracellular adhesion molecule (sICAM-1), human macrophage, chemoattractant protein (MCP-1), and E-selectin. The soluble intracellular adhesion molecule is continuously present in the membranes of leukocytes and endothelial cells and is a marker of endothelial activation (70). Cytokine activation is associated with elevation of sICAM levels, which promotes cellular adhesion and BBB permeability. Individuals with coronary artery syndromes and comorbid depression exhibit significant increases in circulating sICAM concentration (71). Positive associations between cellular adhesion molecule concentration and other metabolic disorders (e.g., DM, obesity) have been documented and are hypothesized to mediate the relationship between cardiovascular disease and metabolic disorders (72).

Chronic pro-inflammatory cytokine activation is also associated with a reduction in neurocognitive performance and abnormal brain activation patterns (7,73,74). For example, elderly persons exhibiting high plasma concentrations are more likely to exhibit a decline in cognitive function. High dose interferon- $\alpha$  therapy in cancer patients is associated with significant reduction in neuropsychological performance and

**Table 1** Shared Pathological Mechanisms in Diabetes Mellitus and Major Depressive Disorder

Proinflammatory cytokines (chemokines, acute phase reactants, cellular adhesion molecules)
Reactive oxygen species (ROS) (cellular respiration)
Glucocorticoid signaling
Intracellular signaling cascades
Genetic
Iatrogenic
Behavioural
Sociodemographic

slower reaction times. In healthy volunteers, low dose interferon- $\alpha$  is also associated with neurocognitive deficits and notably slower reaction times (74).

### *Oxidative Stress*

Reports from several investigations press the point that oxidative stress may be salient to the pathogenesis of mood disorders. The CNS is vulnerable to the effects of oxidative stress due to its high oxidative metabolic activity, polyunsaturated fatty acid content, and relatively low endogenous anti-oxidant capacity (75). Overproduction of reactive oxygen species (ROS) results in oxidative damage, including lipid peroxidation, protein oxidation, and DNA damage which can ultimately lead to cell death (75).

Reactive oxygen species also activate components of intracellular signaling cascades such as mitogen-activated protein kinases (MAPKs) and NF- $\kappa$ B which subsequently activate pro-inflammatory promoter genes (75). Glutathione peroxidase (GP) is an endogenous antioxidant that catalyzes the glutathione redox cycle. Superoxide dismutase (SOD) facilitates the conversion of the neurotoxic  $O_2^-$  into the less toxic  $H_2O_2$  which is further degraded by catalase and GP (76).

The electron transport chain of the mitochondria, the non-enzymatic glycosylation reaction, and hexosamine are the major sources of ROS production in cells. Alterations in mitochondrial respiration are reported in both DM and depressive syndromes and may be a non-canonical target of antidepressant treatment (77,78). The  $\beta$ -cells of the pancreas have relatively low expression of the antioxidant enzymes catalase and GP (78). As a result, the pancreas is susceptible to the toxic effects of oxidative stress mechanisms. For example, the induction of oxidative stress *in vitro* in  $\beta$ -cells suppresses insulin gene promoter activity and mRNA levels. However, the administration of the antioxidant leads to the recovery of insulin biosynthesis and improved glucose tolerance in animal models for type II DM.

Nitric oxide (NO) is involved in multiple actions related to normal, and pathological, CNS function. Nitric Oxide is synthesized from L-arginine by three isoformic enzymes (78). Nitric oxide has been reported to exert both neurotoxic and neurotrophic effects (79). For example, the expression of Inducible nitric oxide synthase (iNOS) has been reported to provoke neuronal cell death and its neuronal expression is increased in persons with Alzheimer's disease (80,81). Nitric oxide is also a free radical and considered to be a second messenger. The physiological effects of NO are largely mediated through activation of the enzyme guanylate cyclase, which produces guanosine 3, 5-cyclic monophosphate (cGMP). The activation of cGMP triggers intracellular signaling cascade which exerts pleiotropic effects on cell function and integrity (78). Although it may be a strong pronouncement that altered NO signaling is a critical component in the pathophysiology (and somatic complications) of MDD and DM, a persuasive body of evidence indicates that NO may be salient to their pathophysiology.

Taken together, oxidative stress is associated with neuronal endangerment and  $\beta$ -cell toxicity. The oxidative stress-mediated activation of signal transduction pathways may underlie the cytotoxic effects documented in both MDD and DM. Treatment strategies capable of reducing oxidative stress constitute biologically plausible treatment avenues.

For example, antidepressant treatment is associated with a decrease in NO concentration and increase in SOD activity. Moreover, thiazolidinedione (TZD) therapy, indicated for the management of Type II DM, has been documented to reduce markers of pro-inflammation and oxidative stress and increase anti-inflammatory/anti-oxidant activity. Historically, the salutary effects of TZDs were first noted as antioxidants. As a possible proof of concept, TZD therapy has been reported to enhance cognitive function in patients with Alzheimer's disease (5).

### *Glucocorticoid Signaling*

Glucocorticoids are counter-regulatory hormones which exert an obverse effect on insulin action (7). The primary role of glucocorticoids and other counter-regulatory hormones are to initiate and sustain a rise in blood glucose in response to stress. The mechanisms involved include gluconeogenesis, glycogenolysis, lipolysis, and inhibition of peripheral glucose transport and utilization (7).

Persons with mood disorders exhibit a high prevalence of Hypothalamic-pituitary-adrenal axis (HPA-axis) disturbances, notably persons with bipolar disorder and psychotic unipolar depression (82). Neuroendocrine studies have shown that up to half of depressed patients are Dexamethasone Suppression Test (DST) non-suppressors (82). These results indicate that mood disorders are associated with disturbances in negative feedback of the HPA-axis. Moreover, post-mortem studies provide evidence of reduced glucocorticoid receptor mRNA expression in post-mortem brain tissue samples from patients with bipolar disorder (83).

It is also reported that there is a direct correlation between peripheral cortisol levels and the severity of depressive symptoms and neurocognitive deficits (84). The hippocampus is a hormonally sensitive organ highly endowed with glucocorticoid receptors (GR). It is hypothesized that the link between HPA dysfunction and somatic toxicity in depression (i.e., allostatis) is mediated through neuronal GR within the hippocampus and other tissues throughout the body.

Taken together, mood disorders are characterized by abnormalities in biomarkers of inflammation, cellular respiration, excitotoxicity, and glucocorticoid signaling which alone, or together, may mediate the effects on neuronal integrity and function. The anti-oxidant effects of TZDs suggest a potential role in altering the neurotoxic biological effects of stress systems on neuronal structure and function.

### **SYNTHESIS AND CONCLUSION**

Although the pathoetiology of MDD (in contradistinction to DM) is not well understood, persuasive evidence indicates that

several interacting biological mechanisms reflecting resilience and adaptation are associated with its clinical presentation. Mood disorders are more precisely characterized as a multi-system syndrome reflecting an imbalance between adaptive and maladaptive mechanisms. Individuals are endowed genetically with unique stress-response mechanisms which are then altered by environmental experiences, particularly early in life (85).

Although a single factor explaining the pathogenesis of depression would be pragmatic, it is unlikely to be comprehensive and coherent. In other words, a single factor explanation is unlikely to sufficiently account for the multiplicity of biological abnormalities associated with, and mélange of symptoms characteristic of mood disorders. Nevertheless, a starting point in an explanatory theory regarding depression may posit that alterations in metabolic networks are a paradigmatic factor in the pathophysiology of MDD. The abnormal metabolic processes in MDD overlap with abnormalities in Alzheimer's disease and DM (e.g., reduced hippocampal volume) suggesting shared pathophysiological mechanisms (86).

A nascent and rapidly expanding literature in both MDD and DM documents overlapping abnormalities in metabolic networks broadly defined as glucose-insulin homeostasis, inflammatory processes, glucocorticoid signaling, oxidative stress, and energy biosynthesis. Admittedly, we are broadly defining metabolic networks in recognition of their highly interactive physiology. From a clinical perspective, refining our understanding of the fundamental mechanisms, which conspire to cause and mediate the clinical expression of MDD, provides an opportunity to develop novel and truly innovative treatments. Extant evidence appears to preliminarily support the notion that select persistent mental illnesses (e.g., MDD, bipolar disorder, schizophrenia) may be independent risk factors for diabetes.

For example, the use of monoamine-based conventional antidepressant treatment was based on a rationale that relative or absolute deficiency in the synaptic availability of monoamines was a critical mediator of depressive symptoms. In keeping with the view that metabolic alterations are salient to the pathophysiology of MDD, treatments which primarily engage components of the metabolic network constitute possible treatment avenues.

Persuasive evidence indicates that antidiabetic agents (e.g., insulin and insulin sensitizers) exert neuroprotective, neurotrophic, anti-inflammatory, and glucocorticoid effects. Preliminary clinical trials have also documented an improvement in neurocognitive performance with the administration of intranasal insulin and oral TZD therapy in populations of patients with Alzheimer's disease. Clinical research is testing the safety and efficacy of an assortment of "metabolic" therapies for the management of mood disorders, notably for neurocognitive deficits (see <http://www.nih.clinicaltrials.gov>).

To recapitulate, alterations in the function of metabolic networks may be a fundamental mechanism in the pathophysiology of MDD. We propose that depressive syndromes could be conceptualized as a pathological process, in which alterations in

metabolic networks are a central feature, i.e., "Metabolic syndrome type II." This conception, we believe, forms the scientific basis for testing "metabolic therapies" for mood disorders.

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