Role of metabolic dysfunction in treatment resistance of major depressive disorder

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Practice points

- Major depressive disorder (MDD) and metabolic syndrome (MetS) are both disorders that cause serious morbidity.
  - We model both disorders as arising when environmental factors act on intrinsic patient risk factors.

- Epidemiological overlap of MDD and MetS: patients with either disorder have approximately doubled incidence of the other.

- MetS and MDD cause overlapping inflammatory, endocrine and neurobiological pathology.
  - MDD and MetS share a systemic profile of inflammatory cytokines and cortisol resistance.
  - Inflammation leads to insulin resistance, cardiovascular disease and diabetes.
  - MetS and MDD are associated with atrophy and dysfunction of several common brain regions.
  - MetS and MDD are both associated with decreased brain-derived neurotrophic factor.
  - Insulin resistance and chronic inflammation impair hypothalamic regulation of metabolism and hippocampal function.
  - MDD and MetS are both associated with changes in tryptophan metabolism that may contribute to medication failure in MDD.

- Clinical research findings that support the treatment of MetS in MDD patients: the direct treatment of metabolic dysfunction or inflammation is very likely to improve depressive symptoms.

- Clinical relevance of the pathophysiological links: we believe that in some patient with treatment-resistant depression, MetS in an unrecognized cause.

- Clinical recommendations: an algorithm for diagnosis and treatment of MetS with patients with depression.

- Future research should focus on validating the importance of MetS in MDD treatment: we suggest studies validating metabolic parameters as predictors of treatment outcome.
SUMMARY  Major depressive disorder (MDD) and metabolic syndrome (MetS) are both widespread and cause enormous morbidity. The presence of one syndrome approximately doubles the risk of the other. Standard antidepressant treatments lead to remission in less than a third of the patients; a majority of patients experience treatment resistance at some point during their illness. Research focusing on clinical and biological markers has yet to provide evidence for the cause(s) of treatment resistance. MDD and MetS share endocrine and immune abnormalities that account for their overlap and suggest potential mechanisms for treatment resistance for a subgroup of patients with MDD. Cortisol resistance and positive energy balance work together to create inflammation. Chronic inflammation leads to insulin resistance. In the brain, inflammation and insulin resistance cause changes in metabolic control, decreases in serotonin synthesis, decreased hedonic drive and lower hippocampal neurogenesis, all of which are consistent with the neurobiology of MDD. We hypothesize that treatment-resistant MDD may result when MetS reinforces the pathophysiology of MDD, making it harder to reverse.

Major depressive disorder (MDD) is the fourth leading cause of disability and is expected to become the second leading cause of disability worldwide by 2020 [1]. MDD affects an estimated 2.5% of the population at any given time [1], with a lifetime prevalence of approximately 20% [2]. Although many different treatments – pharmacologic, behavioral and neurostimulatory – have been developed, MDD remains difficult to manage. Indeed, resistance to treatment is a major problem in contemporary psychiatric practice. Only approximately a third of patients will remit fully with any given trial of medication [3], and the rate of remission drops as the number of medication trials increase [4]. Although definitions of treatment resistance vary [5] in the number and type of failed treatment trials required, approximately 30% of patients with MDD remain resistant to treatment even following several well-documented treatment trials [6]. Much of the confusion over the ‘right’ definition is related to the lack of knowledge – other than some demographic and clinical characteristics [7] – about the differences between those patients who have good outcomes and those who do not. What is known is that patients with treatment-resistant depression (TRD) have higher lifetime illness burden and mortality, as well as a lower quality of life than patients without treatment resistance [8,9]. Understanding the biological mechanisms of TRD would be useful not only in developing a concrete definition, but would also make a large impact on patient outcomes by providing new avenues of research and treatment.

Similarly, metabolic syndrome (MetS) and Type 2 diabetes mellitus (DM2) are common in developed countries, particularly the USA. MetS is defined as a combination of abnormally elevated triglycerides, blood pressure, fasting glucose, increased waist circumference and decreased high-density lipoprotein, with or without a direct or indirect measure of insulin resistance (IR) [10]. MetS has high clinical utility because all of its components, with the exception of IR, can quickly and easily be assessed by clinicians in most practice areas, and because its presence is highly predictive of serious morbidity via stroke, heart attack or other vascular disease [11]. The definition of MetS has evolved over time, and several national and international organizations have developed definitions [12] that differ in clinical feasibility of diagnostic criteria and whether MetS is viewed as simply epidemiological (i.e., predictive of risk) or as a discrete syndrome. The assessed rate of MetS in the USA varies between 23 and 40% depending on the definition used [13]. The term ‘metabolic dysfunction’ may refer to any or all of the aspects of MetS, without reference to specific abnormal values – although less precise, it is used here as a rough synonym for MetS. On the other hand, DM2 is a natural sequela of MetS, resulting when IR progresses such that fasting blood sugar is outside the normal range, affecting 18% of North Americans [14]. In this article, we have chosen to use the term MetS as inclusive of DM2 since all of the pathophysiologic features we discuss later are shared between them. We attempted to find experimental results in human studies that applied specifically to MetS populations; however, in those instances when we were unable to do so, we have used studies of DM2 patients but have specifically noted this fact in the text.

At first glance, a biological link between depression and metabolic dysfunction may seem implausible, since they appear to have differing causes as well as symptoms. To make the link as clear as possible, we start with a model of MDD as a disorder that occurs when intrinsic genetic and
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epigenetic susceptibilities of an individual are acted upon by the individual’s environment; we also have a similar model of MetS. In this article, we will deal almost exclusively with extrinsic factors and present evidence that these cause similar pathology in patients. We will also discuss how we believe that the common pathology may lead to treatment resistance. We hypothesize that in cases in which both syndromes are present, they exert additive physiological effects that lead to a lower probability of positive outcomes for treatment for either syndrome. To support our hypothesis that MetS is likely an underappreciated cause of TRD, we will focus on mechanisms – both peripheral and central – by which MetS may reinforce depression symptoms and pathology, as well as interfere with the action of antidepressant treatment.

Simplifying somewhat, we will take the primary exogenous factor in MetS to be chronic positive energy balance (PEB), a state in which more calories are consumed than expended. For MDD, the primary environmental influence appears to be chronic or severe stress. We will begin by reviewing epidemiological studies that demonstrate high comorbidity of MetS and MDD. Next, we will discuss significant similarities in how the endocrine and immune systems respond to the two environmental factors, stress and PEB, and how this leads to similar profiles of cytokine and hormone abnormalities in those with MDD and MetS. Following the examination of systemic dysfunction, we will look at common structural and functional changes that occur in the brains of those with MDD and MetS. We will also discuss some of the pathophysiological mechanisms underlying these abnormalities in an effort to demonstrate that the presence of one of these disorders creates positive feedback that may make the other more difficult to reverse.

Epidemiological overlap of MDD & MetS

Major depressive disorder and MetS share many qualities: both are chronic, cause high morbidity and require sustained, coordinated treatment that manages rather than cures. However, beyond the superficial similarities, there is a significant epidemiological overlap between them. Both cross-sectional and longitudinal studies have found that having depression approximately doubles the rate of MetS [15–18] and vice versa [19,20], although some authors have found an elevated, but not doubled, risk of MDD in DM2 [21,22]. Several studies found that subjects reporting high levels of stress with or without MDD had similarly elevated MetS rates [18,23]. Rates of TRD in patients with MetS have not accurately been determined – few placebo-controlled studies of treatments exist, and those that do have small sample sizes [24,25].

Shared systemic profile of inflammatory cytokines & cortisol resistance in MetS & MDD

Inflammation has emerged as a major, if not the primary, pathophysiological link between MDD and MetS [26]. An inflammatory model of MetS that begins with changes in metabolic activity of adipose tissue as it increases in volume has become increasingly validated with ongoing research. In response to chronic PEB, adipocytes produce factors that recruit macrophages and decrease the number and/or function of anti-inflammatory Tregs [27,28]. Adipocytes also begin to produce the proinflammatory cytokines IL-1β and TNF-α. These attract macrophages and incline them to switch from an anti-inflammatory M2 state to a proinflammatory M1 state, in which they produce the same cytokines, as well as IL-6 [27]. It appears that these inflammatory processes are enhanced by leptin, an ‘adipokine’, which is an immunologically and metabolically active factor produced by adipocytes. Leptin serves as a signal of energy balance, and is high when energy balance is positive [29]. In ongoing PEB, high leptin directly activates macrophages and induces their expression of inflammatory cytokines [30]. This cascade in turn recruits more macrophages, which stimulate further cytokine production in a feed-forward manner, setting up a chronic inflammatory state. Clinically, this is reflected in elevations of circulating TNF-α, IL-1β and IL-6 in the blood of MetS patients [31–34].

This same cascade of macrophage-associated inflammation occurs in MDD. It has been hypothesized that MDD itself is an inflammatory illness [35]; certainly, inflammation caused by autoimmune disease or administration of cytokines (such as IFN-γ for the treatment of hepatitis C) induces depression in a sizable minority (30–50%) of patients [36,37]. Even depressed patients without known autoimmune or infectious processes have elevated levels of M1 inflammatory cytokines, with IL-6 and TNF-α having the most consistent evidence [38]. Although cortisol is acutely anti-inflammatory, MDD- or chronic stress-associated cortisol resistance, as manifested by glucocorticoid receptor (GR) insensitivity, leads to activation of proinflammatory pathways that are normally suppressed.
by cortisol [39,40]. Once activated, macrophages can also support chronic stress induced hypercortisolemia; exposure to IL-1β can activate expression of adrenocorticotropic hormone from macrophages themselves [41], as well as via the hypothalamus [42]. Thus the effects of stress are synergistic with PEB-associated inflammation; the two feed forward to create a chronic state of inflammation and high systemic cortisol and/or cortisol resistance. The changes in inflammatory factors that are in common with MetS and MDD are listed in Table 1.

While it is clear that chronic elevations of cortisol can cause IR – this is the basis of high rates of diabetes in patients with Cushing’s disease [43] – the role of cortisol and GR insensitivity in most cases of MetS is less straightforward. Basal levels of cortisol may be normal in MetS; however, if corticosteroid suppression testing is performed, GR insensitivity is often found [44,45] – the variability in cortisol levels is likely accounted for by increased cortisol clearance in obesity [46].

### Inflammation leads to IR

If this chronic inflammatory and cortisol resistant state persists, it leads to IR, which occurs by several mechanisms. First, cortisol decreases insulin-mediated expression of the GLUT4 glucose transporter – the primary systemic transporter of glucose into cells – by decreasing insulin receptor activity [47]. Similarly, cortisol promotes release of free fatty acids from lipoproteins [48], leading to an increase in circulating lipids. Free fatty acids also cause decreased sensitivity of the insulin receptor, particularly on muscle cells [49]. Chronic elevations of inflammatory cytokines, particularly TNF-α, cause similar, additional suppression of insulin receptor signaling [50]. An additional mechanism of IR is a PEB-associated decrease in the expression of adiponectin, another adipokine. Unlike leptin, adiponectin levels are inversely related to body weight, and it appears to promote insulin sensitivity [51,52] and oppose the MetS-associated inflammatory cascade [53]. Adiponectin-knockout mice are not diabetic at baseline but develop IR more easily when fed diets that induce PEB [54]. Cytokines, particularly TNF-α, can also act to decrease expression of adiponectin [55], such that lower levels are found in MDD patients independent of weight [56,57]. The overlap in these mechanisms suggests that weight-independent IR may be found in patients with MDD. In fact, outside of the population of patients with comorbid MetS and MDD, a significant minority of patients with MDD alone show IR when given oral glucose tolerance testing [58]. Figure 1 summarizes the peripheral inflammatory changes associated with MetS and MDD.

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**Table 1. Shared inflammatory changes in major depressive disorder and metabolic syndrome.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Change in MetS</th>
<th>Change in MDD</th>
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<tbody>
<tr>
<td>Adiponectin</td>
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<tr>
<td>IL-6</td>
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<tr>
<td>TNF-α</td>
<td>+</td>
<td>+</td>
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<tr>
<td>IL-1β</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Leptin</td>
<td>+</td>
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<tr>
<td>Insulin</td>
<td>+ (resistance)</td>
<td>+ (resistance)</td>
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<tr>
<td>Cortisol</td>
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CRP: C-reactive protein; MDD: Major depressive disorder; MetS: Metabolic syndrome.

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**Chronic inflammation leads to morbidity from cardiovascular disease & DM2**

Over time, if the environmental influences of stress and PEB continue, inflammation leads to vascular disease – the major cause of morbidity associated with MetS. Patients with MDD also have higher rates of morbidity/mortality from cardiovascular disease [59]. The general inflammatory marker C-reactive protein is also consistently increased in MDD [60] and MetS [61,62]. This increase in C-reactive protein is associated with elevation in a wide variety of factors that contribute to the development of arteriosclerosis [63]. Cardiovascular disease risk is elevated threefold in patients with MetS [14], making this the primary cause of serious morbidity and mortality in MetS. When there is systemic IR, the pancreas compensates by increasing insulin output, but over time diabetes develops because blood glucose can no longer be kept within the normal range. Feed-forward IL-1β signaling occurs within the pancreas and sets up chronic, local islet inflammation, which leads to islet cell death, and eventually patients require supplementary insulin [64].

**MetS & MDD are associated with atrophy & dysfunction of several common brain regions**

Although we have so far focused on systemic pathology, MDD at least is thought of as a brain disease, and has been characterized by both structural and functional changes in the brain. While MetS may have its roots in adipose tissue,
it also causes brain changes that overlap anatomically to a large extent with those associated with depression. Perhaps the most consistently identified structural abnormality in MDD is hippocampal atrophy [65]. Some studies also have found thinning of the prefrontal cortices [66]. It has been debated whether this atrophy represents an underlying vulnerability to MDD [67] or an effect of the illness [68], but these areas are clearly part of the biological substrate on MDD. A similar pattern of hippocampal and prefrontal atrophy is seen in MetS and DM2 [69,70]. BMI itself is positively correlated with decreased hippocampal volume and frontal cortex thickness [71].

The consequence of brain atrophy is reduced cognitive function in patients with MDD and MetS. MDD is associated with decreased attention and verbal working memory [72]. MetS is found to correlate with similar deficits [73,74]. Both syndromes have been associated with an increased risk of dementia [75,76]. At least some authors have found that comorbid MDD and MetS is associated with more impairment than either alone [77]. IR has been isolated from the other components of MetS as the most associated with cognitive decline [74,78] and is correlated with decreases in blood flow in frontal cortical areas [79]. Hippocampal atrophy and impaired hippocampal learning are both associated with normal aging [80], and some authors have proposed that inflammation plays a significant role in the accelerated cognitive decline associated with MDD and MetS [81]. Figure 2 shows the putative relationships leading to hippocampal dysfunction.

Changes in growth factor expression (see later) and accumulation of microvascular damage over the lifespan may contribute to these structural abnormalities, but clearly some common factors in MDD and MetS that we have already discussed play a role by acting in the brain much as they do systemically. For example, inflammatory cytokines appear to increase the activity of the serotonin transporter [82], possibly impairing serotonin neurotransmission and decreasing the efficacy of selective serotonin-reuptake inhibitors (SSRIs). However, perhaps the most important of these is central IR, which develops in association with peripheral resistance. Insulin

Figure 1. Network showing the links between metabolic syndrome and depression via inflammation. HPA: Hypothalamic-pituitary-adrenal; IDO: Indoleamine-2,3-dioxygenase.

Figure 2. Diagram showing the relationships leading to hippocampal dysfunction.
is important in the hippocampus because insulin receptors mediate changes in glutamate neurotransmission – a form of long-term depression that plays a role in memory and cognitive function – and promote growth of synaptic architecture and dendritic spines [83]. In fact, intranasal insulin administration improves cognitive function in normal controls [84] and those with mild dementia [85] and may also improve mood [86]. Cortisol is also known to cause hippocampal dysfunction by several mechanisms. It induces increases in NMDA receptor glutamate neurotransmission, which are thought to be neurotoxic over long time periods, making growing hippocampal cells more vulnerable to apoptosis. It also causes decreased dendritic arborization and synaptic plasticity [87]. As in the periphery, cortisol also synergistically downregulates insulin receptor signaling [88], contributing to the effect of CNS IR.

MetS & MDD both decrease expression of brain-derived neurotrophic factor

An additional mechanism is tied to brain-derived neurotrophic factor (BDNF) – a growth factor that is already well known as a primary mediator in the hippocampal dysfunction related to depression. It appears to be necessary to maintain hippocampal neurogenesis and it promotes synaptic growth and arborization in neurons [89,90]. Although the relationship between central and peripheral BDNF is not fully understood, serum BDNF is low in MDD [91] and is thought to reflect a decrease in central, particularly hippocampal, BDNF expression. The exact mechanisms that cause low BDNF in MDD are not fully understood, although various stress paradigms in animals result in decreased hippocampal BDNF [92], and cortisol appears to suppress neuronal BDNF gene expression [93]. However, antidepressants appear to require BDNF expression in the hippocampus for efficacy [94], so low BDNF may predispose to treatment failure – mice with lowered BDNF expression do not respond to SSRI treatment neurochemically or behaviorally [95]. However, these mice display an aggressive rather than depressed phenotype [96], and humans with genetically decreased BDNF expression do not clearly manifest TRD, although this relationship has been abundantly examined [97]. These results potentially suggest that genetic differences in BDNF expression may not affect the brain in the same way as environmentally
induced changes, but ultimately highlight that the clinically relevant effects of BDNF in MDD are still unclear.

The body of literature linking decreased BDNF to MetS is less well known to psychiatrists, but consistently links decreased BDNF to dysfunction in metabolic control. PEB induced through a high-fat diet causes a decrease in hippocampal BDNF expression in mice, as well as decreased neurogenesis [98]. As with MDD, human subjects with MetS have lower levels of peripheral BDNF [99,100], which improves with correction of PEB through dieting [101]. It appears that in humans, genetically determined decreases in BDNF, whether due to functional deletion [102–104] or allelic variation [105,106], are associated with obesity and hyperphagia. Centrally, BDNF plays a role in the hypothalamic control of appetite and eating behavior by modulating the appetite-lowering response to high-fat-containing meals [107]. It also appears to potentiate dopamine responses to food rewards [108]. In addition to its central role in mood and metabolic regulation, BDNF also appears to promote development of muscles and peripheral nerves in response to exercise [109] and may thus connect physical activity to improvements in mood as well as metabolic improvement. It appears that both MDD and MetS are associated with decreased BDNF expression, and that, at least in the case of MetS, decreases in BDNF can be a primary cause. A drop in BDNF related to MetS could thus reasonably lead to TRD by blocking antidepressant-induced neurogenesis in the hippocampus.

**IR & chronic inflammation impair hypothalamic regulation of metabolism**

Insulin receptors are expressed in the hypothalamus as part of its role in regulating metabolism and appetite [110]. It also sits at the ‘top’ of the hypothalamic–pituitary–adrenal axis and provides central regulation of the stress response. This combination places it critically in the network linking MDD and MetS, relationships that are depicted in Figure 3. Normally, the hypothalamus maintains bodyweight by modulating metabolic rate and appetite according to current energy needs. Insulin and leptin both act on the arcuate nucleus to signal current energy status [111]. However, under conditions of chronic PEB, the same macrophage-associated inflammatory cascade that causes IR in the periphery occurs locally in the hypothalamus and leads to insulin and leptin resistance [112]. Decreased insulin and leptin receptor signal transmission results in maintenance of appetite and bodyweight despite ongoing PEB. This appears to account for the difficulty many obese people have in losing meaningful weight – chronic central changes have reset the body’s metabolic regulatory mechanism to favor obesity [111]. Although less-rigorously validated, patients with MDD may experience a similar kindling phenomenon in which each depressive episode increases the probability of future depression [113].

One possible mechanism through which these inflammatory changes in the hypothalamus could affect mood is via orexin. Orexin was first discovered as the key component lacking in animal and human narcolepsy; it plays a central role in maintaining arousal [114]. However, narcoleptics also display metabolic abnormalities – increased weight despite lower food intake [115] – that suggested orexin influences energy metabolism. Orexin is made in neuronal cell bodies in the lateral hypothalamus [116] whose axons project widely over the brain [117], including the raphe nuclei and locus ceruleus. Orexin activity responds to the nutritional state over short time frames, such as when blood sugar and/or leptin is low [114]. Orexin increases arousal and food-seeking activity by raising serotonergic and noradrenergic tone. Serotonin and norepinephrine in turn can inhibit orexin release [118]. Orexin neurons also project to the ventral tegmental area of the midbrain where they increase dopamine reward signaling [119]. Orexin appears to mediate parts of the acute stress response that is impaired in orexin-knockout mice [120]. The exact relationships between orexin, metabolism and mood remain to be elucidated, but animal studies have demonstrated that orexin can block chronic stress-induced depression-like behavioral changes in mice [121] and that this mechanism is dependent on leptin. This suggests that obesity-related leptin resistance may leave patients less resilient to stress. In addition, since orexin increases signaling of monoamine transmitters, lack of its activity may lead to anhedonia or make antidepressants less effective. While research in this area is still in fairly early stages, understanding the orexin system has the potential to greatly improve our understanding of the central connection between metabolism and mood.
Changes in tryptophan metabolism may cause medication failure in MDD

The inflammatory cytokines share an additional mechanism with stress-induced hypothalamic–pituitary–adrenal axis hyperactivity that is an appealing possible explanation for TRD in those with MetS. Cortisol, TNF-α and interferon all induce one or both of the enzymes indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase [36,122]. These enzymes shift the metabolism of tryptophan away from synthesis of serotonin and toward kynurenine. Increased peripheral metabolism of tryptophan by IDO and tryptophan-2,3-dioxygenase creates a state of relative tryptophan depletion, and alters the ratio of tryptophan to kynurenine and its metabolites in the brain [123].

Acute experimental induction of tryptophan depletion appears insufficient for the induction of MDD in healthy people, but can reverse symptomatic improvements from SSRI treatment in those with depression [124,125]. Although patients with MDD may have lower circulating tryptophan than controls [126,127], no large, well-controlled studies have examined whether supplementation improves treatment outcome [128]. In addition, while IFN-γ appears to be the primary mediator of IDO induction [129], patients with MDD do not appear to have higher IFN-γ levels than controls [38]. This may mean that cortisol and other regulators are more important in activating IDO in most depressed patient with low tryptophan. However, this pathway does have good evidence of relevance for those who are treated with cytokines. First, the behavioral importance of IDO induction due to interferon is supported by the finding that mice that do not express IDO are resistant to the depression-like, but not the sickness-like, behaviors caused by an inflammatory stimulus [130]. Second, in cancer patients treated with IFN-γ, a drop in circulating tryptophan correlates with depression symptom severity [131].

There is also good evidence that IDO induction occurs in MetS. Plasma tryptophan is low in obese subjects [132] and is thought to be related to adipose tissue inflammation-induced IDO activation [133]. While few studies have directly measured IFN-γ levels in MetS, and in those that have, the results have been mixed [62,134], it appears more certain that the low tryptophan in MetS is mediated by IDO [135]. Inflammation- and IDO-mediated tryptophan depletion may also feed forward to maintain PEB because
serotonin also mediates satiety – those with low tryptophan may be more likely to over-eat [133]. Tryptophan depletion associated with MetS could potentially induce or worsen depression, and to the extent that experimental depletion acts as a model, this depletion could have negative impacts on treatment.

Clinical research findings that support the treatment of MetS in MDD patients

The common pathology described earlier leads to the question of whether the treatment of MetS can be used to address the treatment of MDD. IR is a possible subclinical feature of MDD, as described earlier. Several studies have examined whether IR in patient with MDD but not MetS responds to antidepressant treatment [136–139] using oral glucose tolerance testing (OGTT). The fact that all of these studies found improvements in IR with antidepressants strongly supports conceptualizing metabolic dysfunction as a feature of MDD. In one study, the outcome was specifically linked with improvement on OGTT [139], suggesting that IR may function as a moderator of treatment. However, further research is needed to clarify whether the clinical relationship between MDD and MetS is bidirectional or if it is more meaningful in one direction only. Nonetheless, taken together, these studies imply that in patients with TRD, it is reasonable to consider testing for IR even in the absence of full criteria for MetS, as well as studying treatment responses in patients in whom it is found.

Addressing the issue from the opposite direction, some studies examining the effects of metabolic medications on depression have already been performed based on the evidence of pathophysiological overlap. The thiazolidinediones (pioglitazone and rosiglitazone), which improve insulin sensitivity, have shown antidepressant effect in rodents [140] and are beginning to be studied in human subjects. In one published case, a patient with severe TRD and subclinical IR improved dramatically with pioglitazone [141]. Similarly, in a small pilot study, eight out of 12 patients who received augmentation treatment with rosiglitazone showed improvements in mood [142].

It may also be possible for medication to act at on inflammation that links MDD to MetS – several trials of antidepressant treatments have found elevated cytokines are associated with failure to respond [143–145]. In this vein, the group of TNF-α inhibitors recently approved to treat rheumatoid arthritis and other autoimmune diseases have also generated some interesting data regarding their possible use in patients with TRD. Groups of patients with psoriasis [146] and ankylosing spondylitis [147] showed improvements in symptoms of MDD when treated with TNF-α antagonists, effects that were measured separately from illness burden and fatigue. These drugs may also improve metabolic markers in MetS [148], suggesting that for severe and/or comorbid cases, they may be worth further research despite their side effects.

Clinical relevance of the pathophysiological links

There is significant clinical and pathophysiological overlap between metabolic derangement and depressed mood. More specifically, systemic inflammation and IR in MetS predispose to depression through central IR. Decreased insulin signaling in the brain is synergistic with stress-related inhibition in GR function and creates abnormalities in serotonin signaling, reward circuitry and hippocampal cognitive function. Metabolic dysfunction in patients with MDD certainly leads to entrenchment of pathophysiology. It may also interfere directly and indirectly with the actions of antidepressants through inhibition of growth factors and interference with monoamine neurotransmission. Although the specific clinical effects of these interactions have not yet been adequately studied, because of the high comorbidity and similar underlying pathophysiology, we believe that MetS is likely to be a significant source of treatment resistance in depression. We suggest that clinicians should be aware of MetS in their patients and consider medical management of MetS.

Clinical recommendations

Based on the biological connections between MetS and MDD, we recommend that clinicians aggressively cross-screen patients with either MDD or MetS. These recommendations are presented as an algorithm in Box 1. Because of growing concern about specific metabolic effects of certain psychiatric medications, it has already become more common for psychiatrists to monitor metabolic status in their patients. However, the connection between MetS and MDD suggests that all patients with depression could benefit from screening regardless of treatment type. The major components of MetS can be measured easily in the office at every visit – BMI, waist circumference and blood pressure – and laboratory
testing of lipids is easy to perform on a periodic basis. Referrals to primary care providers should be made for cases in which the psychiatrist is not comfortable managing metabolic abnormalities. Even in the absence of direct clinical evidence that metabolic treatment will improve mood, it certainly will reduce the long-term risk of morbidity and be of benefit to patients.

While many factors have been associated with occurrence of TRD, few of them are modifiable at the time a patient sees a psychiatrist. Genetics and childhood experiences are fixed, and patients have often been depressed for years or have had multiple episodes. MetS, on the other hand, has numerous approved medications already on the market for its treatment, in addition to evidence-based lifestyle modifications. The long and expensive process of drug development would not be needed if aggressive management of comorbid MDD and metabolic dysfunction is found to be effective – treatment algorithms could be moved almost immediately into clinical practice, where they could profoundly effect treatment outcome for many patients.

Since exercise has been independently shown to dramatically reduce progression from MetS to DM2 [149] and to improve the majority of cases of DM2 [150] and many cases of MDD [151–154], exercise should also be considered as a viable treatment either alone or in conjunction with antidepressant medications for patients with comorbid illness. Structured exercise and behavioral modification programs may prove to be worth the extra upfront expense in these patients by increasing adherence, and thus benefit.

Future perspective: we should focus on validating the importance of MetS in MDD treatment

Although clinical decision-making can be guided to some extent by currently known information, there remains no clearly established link between treatment resistance per se and MetS. Although there are several possible mechanisms, it remains to be determined which are the most relevant clinically. We propose that patients with comorbid MetS (and perhaps those with subclinical MetS features) are a distinct subtype of depressed patient who may benefit from specialized treatment that is superior to usual care of MDD plus usual care of metabolism. Studies examining treatment outcomes in this subgroup specifically would be of great value in determining unique treatment characteristics and defining rates of TRD. Currently, while mood symptoms may be measured as a secondary outcome in large studies of metabolic disease, few groups within psychiatric research focus on the study of patients with medical illness-associated depression. These patients may be found to respond more to particular medications or to other types of treatments. Studies comparing symptom profiles, response/remission rates and biomarkers of depressed patients with comorbid metabolic disturbance with those without these features may further define this group of patients and lead to enhanced personalized treatment.

However, some MDD patients will not meet criteria for MetS, as it is currently defined, but will have elevations in cytokines and IR. Although, as mentioned earlier, MDD-associated IR has been shown to improve with antidepressant treatment, no study has yet attempted to determine if IR is a predictor of TRD, nor has any study compared response rates between patients with MDD who differ in the presence or severity of IR. If IR reduction is beneficial to outcome, it is possible that these patients would demonstrate additional improvements in depressive symptoms if treated with metabolic or anti-inflammatory agents. Testing patients with TRD with OGTT for IR, or drawing blood for cytokine levels, is not burdensome and would select a target population. An open-label study

**Box 1. Treatment algorithm for diagnosing and treating metabolic syndrome in patients with major depressive disorder.**

- Collection of a thorough medical, psychiatric and medication history
- Measurement of blood pressure, weight and waist circumference
- Laboratory assessment of blood glucose and lipids
- Diagnosis of metabolic syndrome, if present
- Prescription of appropriate medication(s), appropriate referral to primary care providers and specialists to manage metabolic abnormalities, and suggestion of lifestyle changes (diet and exercise)
- Assessment of antidepressant response over 4–12 weeks
- Continued monitoring of metabolic criteria and mood symptoms
in which patients with MDD and IR are treated with antidepressants and then randomized to a metabolic agent versus placebo to directly compare remission rates would provide results of high clinical utility and be straightforward and low risk to conduct.

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Bibliography
Papers of special note have been highlighted as:

- of interest
- of considerable interest


- Outcomes of the STAR*D study, demonstrating real-world response and remission rates to antidepressant treatment.


- Looks at outcomes for subjects in the STAR*D study who required multiple treatment trials.


- Examination of the characteristics of patients with successful and unsuccessful treatment for major depressive disorder (MDD).


- Comprehensive and accessible review of metabolic syndrome.


Role of metabolic dysfunction in treatment resistance of major depressive disorder

REVIEW
Examination of the role of inflammation plays in connecting adiposity to mood disturbance.


Meta-analysis confirming elevations of peripheral cytokines in MDD.


Clear summary of hippocampal abnormalities seen in MDD.


Behavioral and serotonergic consequences of decreasing or increasing hippocampus brain-derived neurotrophic factor protein levels in mice. *Neuropharmacology* 55(6), 1006–1014 (2008).


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Comprehensive review of the various brain functions of orexin.


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