Role of corticosteroids in the antidepressant response

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Abstract: Anything that engenders a homeostatic response in the tightly regulated hypothalamic–pituitary–adrenal (HPA) axis may be thought of as a stressor and may exert an allostatic load, engendering a sustained change in the regulation of this system. Genetic, epigenetic, endocrine, post mortem, and animal studies suggest that dysregulation of the HPA axis plays a part in the pathophysiology of mood disorders and negatively impacts the antidepressant response and prognosis. Neuropsychological impairment, which is a common and disabling concomitant of depression, has been linked to disturbance of the HPA axis. A number of HPA axis-mediated treatment strategies have shown benefit in open or small-scale preliminary trials, and there are ongoing studies seeking both to replicate these initial findings and to develop new targets. HPA axis-based treatments are a fertile area of research, and much current thought pertains to the optimum targets, optimum population (including the potential for stratified medicine), and optimum outcome measures. We have, for instance, argued here that neuropsychological performance may be more sensitive and robust than scores on traditional depression rating scales.

Keywords: hypothalamic–pituitary–adrenal axis, cortisol, corticotrophin-releasing hormone, arginine vasopressin, depression, bipolar disorder, antidepressant response

Introduction

Depression is one of the major debilitating illnesses facing the modern world and the leading chronic mental health condition.¹ The global disease burden is shifting away from premature deaths and towards chronic conditions, hence depression and depressive conditions cause a progressively greater disability adjusted life-years burden.¹ Moreover, societies in the developed and increasingly in the developing world are ageing, so chronic conditions are more prevalent and confer a greater financial burden. In England in 2007, the cost to health services of managing patients with depression was £1.7 billion. Adding the cost of lost employment, the figure becomes £7.5 billion and is projected to rise to £12.2 billion by 2026.²

Current treatments provide full remission after first-line antidepressants for only one third of patients.³ The physiological and biological causes of depression are not fully understood, and this is at least part of the reason why treatment is not successful in a substantial number of cases. In this paper, we review the evidence that the hypothalamic–pituitary–adrenal (HPA) axis is dysregulated in depression and outline the potential impact and its consequences. We also look into the evidence base for drugs that target the HPA axis.
**Physiology of the stress response**

Depression has been identified as one of the major outcomes of stressful situations, and Hans Selye (1907–1982) defined stress as “the non-specific response of the body to any demand placed upon it”. This definition was further expanded by Bruce McEwen, who described stress as “experiences that are challenging emotionally and physiologically”. He also stated that “a hallmark of the stress response is the activation of the autonomic nervous system and hypothalamic–pituitary–adrenal axis”. He argued that these biological factors, which mediate the effects of stress on the body, have protective and adaptive effects but can become detrimental in the long run. He thus introduced the concept of allostasis.

The HPA axis, which comprises the hypothalamus, pituitary gland, adrenal cortex, and associated releasing factors and hormones, has both neuronal and endocrine functions (Figure 1). It is influenced by afferent projections from numerous structures, including the limbic system, and it contributes to regulation of the immune system, energy release and storage, sleep, and sexual function. Corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP), released from the paraventricular nucleus of the hypothalamus into the hypophyseal portal system, act on membrane type 1 CRH and on vasopressin receptors in the anterior pituitary lobe to stimulate the release of adrenocorticotropic hormone (ACTH). ACTH in turn stimulates the production of glucocorticoids in the zona fasciculata of the adrenal cortex. The rate-limiting step in cortisol synthesis is the transfer of cholesterol into the mitochondria. The subsequent metabolism of cholesterol relies on a number of adrenal enzymes. For example, 21-hydroxylase catalyses the conversion of progesterone to 11-deoxycorticosterone and 17 hydroxyprogesterone to 11-deoxycortisol that is further metabolized by 11β-hydroxylase to cortisol (Figure 2).

Cortisol is released into the circulatory system in a diurnal fashion. The level peaks early in the morning around 8 am with a concentration of approximately 20 µg/dL. It reaches its trough level of approximately 5 µg/dL around 4 pm. A number of factors impact receptor availability of cortisol. The majority of cortisol in the circulation is bound to corticosteroid binding globulin. Permeability glycoprotein-1 acts as an efflux pump and actively transports cortisol out of cells. It has a relatively high expression in

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**Figure 1** Hypothalamic–pituitary–adrenal axis.

**Notes:** + represents positive feedback, – represents negative feedback.

**Abbreviations:** ACTH, adrenocorticotropic hormone; MR, mineralocorticoid receptor; GR, glucocorticoid receptor; CRH, corticotrophin-releasing hormone; AVP, arginine vasopressin.

**Figure 2** Glucocorticoid biosynthetic pathway.

**Abbreviations:** DHEA, dehydroepiandrosterone; HSD, hydroxysteroid dehydrogenase.
the adrenal gland. Two isoenzymes, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and type 2 (11β-HSD2) regulate glucocorticoids at the tissue level. 11β-HSD1 converts cortisol to cortisone, whereas 11β-HSD2 converts cortisone to the relatively inactive cortisone.

Cortisol has a wide range of both central and peripheral effects, including effects on energy metabolism and on immune and inflammatory responses. These effects are mediated by at least two intracellular, specialized steroid receptor subtypes, i.e., the high-affinity type I mineralocorticoid receptor (MR) and the low-affinity type II glucocorticoid receptor (GR). GR is a member of the superfamily of nuclear hormone receptors and is a ligand-dependent transcription factor, expressed as an intracellular protein. After ligand binding, the GR translocates from the cytosol to the nucleus where it modulates the activity of glucocorticoid response elements and thus regulates gene transcription. The GR binds to and inactivates other transcription factors, such as nuclear factor kappa beta and AP-1, and thus exerts an anti-inflammatory response. This activation and translocation process and subsequent GR-mediated gene transcription is regulated by heat shock proteins 70 and 90 and their chaperones, such as FK506 binding protein 1 (FKBP5) and BCL2 associated athanogene. FKBP5 impedes GR activation, and when FKBP5 is bound to the receptor complex, cortisol binds with lower affinity and the nuclear translocation of the receptor is less efficient.

The HPA axis is under homeostatic control, so activation of MR and GR causes feedback inhibition of the HPA axis at the hippocampus, hypothalamus, and the anterior pituitary gland, and facilitation by the amygdala. In addition, GR activation induces FKBP5 mRNA and protein expression and this provides an ultrashort feedback loop to rapidly decrease GR sensitivity. Variants in the FKBP5 gene are associated with differential protein expression. High induction alleles are associated with relative GR resistance.

There is a reciprocal relationship between the HPA axis and the monoamine systems. Serotonin neurons originate in the raphe nuclei, which are located in the midline of the brain stem. Serotonergic neurons ramify widely and terminate throughout the brain and in the spinal cord. The hippocampus expresses corticosteroid and serotonin (5-HT) receptors, and is considered to be a focal point of the interaction. Both 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> are highly expressed in the hippocampus and are involved in HPA axis regulation. Hippocampal expression of 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors have been shown to be altered by glucocorticoids. Altered 5-HT function in the hippocampus has been suggested as a cause of abnormal changes in the negative feedback mechanism to glucocorticoids in depression. Hippocampal cultures from fetal guinea pigs exposed to 5-HT showed a significant increase in GR mRNA levels, suggesting that early exposure to 5-HT can affect GR expression within the hippocampus during development and can lead to permanent reprogramming of the HPA axis.

The HPA axis plays a central role in regulating a range of physiological functions. The system has built negative feedback loops that prevent excessive release of the primary stress hormone cortisol from the adrenal cortex. Whilst the human body has the capacity to manage and maintain an allostatic response, it is believed that permanent structural changes can occur in the HPA axis, leading to a dysfunction which is manifested in an inability to adapt to stress and dysregulated hormonal levels. HPA dysfunction is in turn believed to be associated with a reduced response to antidepressant medication and a worse prognosis.

**HPA axis and monoamine function in patients with mood disorder**

The role of the HPA axis in the pathogenesis of depression and mood disorders in general has been extensively investigated. Cross-sectional endocrinology studies suggest that HPA axis dysregulation is a common although not inevitable finding in depressed patients. However, its prevalence is greater amongst in-patients and individuals with severe episodes of melancholia or psychosis. Studies have been performed to measure basal cortisol levels in urine, blood, and saliva at single time points, as well as sequentially in order to determine whether diurnal variation or a waking response exists. Saliva assays of HPA axis hormones have proven reliable and noninvasive, less likely to induce a stress response, and more consistent in response to suppression testing. The so-called “activated tests” are more sensitive than basal measures. Examples are measurements of cortisol before and/or after a pharmacological challenge with agonists or antagonists of CRH, AVP, ACTH, MR, or GR. This could be done either individually or in combination (eg, the dexamethasone/CRH test) or after psychological stressors, eg, the Trier Social Stress Test. The most reliable finding to emerge from studies of the HPA is the presence of reduced GR functional activity, often referred to as glucocorticoid resistance. The interindividual variability in the outcome of HPA axis function tests in patients with psychiatric syndromes has led some to argue for the use of HPA axis-defined subgroups with the prediction that this development may lead to a more rational choice of treatment strategy.
The relevance of HPA axis dysregulation in mood disorders and especially in depression is exemplified by the results of studies investigating patients with primary endocrine abnormalities. Neuropsychiatric symptoms, including depressed mood, are common in both Cushing’s disease and Addison’s disease. Cushing’s disease is characterized by increased secretion of ACTH from the anterior pituitary. Pituitary adenomas or elevated production of hypothalamic CRH may cause this pathology. Addison’s disease is a disorder of the adrenal cortex resulting in inadequate secretion of glucocorticoids and mineralocorticoids. The mood symptoms associated with both these conditions respond well to normalization of steroid production.

Post mortem studies of individuals with a history of depression and those who committed suicide have been used to investigate the hypothesis that depression is associated with HPA dysfunction. Studies have shown reduced MR expression in the hippocampus, increased MR expression in the hypothalamus, as well as reduced GR expression in the cingulate gyrus, inferior frontal gyrus, prefrontal cortex, and front and inferior temporal cortices. This concurs with animal studies that showed downregulation of GR mRNA expression in the hippocampus and frontal cortex in rodents with hypercortisolism. Interestingly, one study showed that hippocampal GR mRNA in depressed patients did not differ from matched controls that reported chronic stress. Selective abnormalities of GR mRNA expression in the orbitofrontal cortex and alterations in protein isoforms have been noted in a range of psychiatric conditions. Post mortem studies of depressed patients who committed suicide have also shown a reduction in CRF receptor sites in the cerebral cortex.

Whether HPA axis dysregulation is a cause, consequence, or an epiphenomenon of depression can be determined by considering an individual’s genetic profile. The observation that depression tends to cluster in families suggests that genes play an etiological role. It is possible that some of this risk is attributable to the genes coding for HPA axis proteins, given a 62% heritability of basal cortisol concentrations. This is in addition to the finding that apparently healthy first-degree relatives of probands with major depressive episodes exhibit HPA dysregulation similar to that seen in affected relatives and different to the response seen in healthy controls. The failure of genome-wide association studies to identify relevant genetic polymorphisms (or for that matter any polymorphisms) associated with the HPA axis is likely attributable to the complex relationship between the environmental and genetic factors that predispose to depression. However, candidate gene approaches yield interesting results. For example, polymorphisms of the FKBP5 gene affect GR sensitivity and hence the stress hormone response.

Individuals carrying alleles and haplotypes associated with GR resistance have been shown to have increased vulnerability to depression, bipolar disorder, and post traumatic stress disorder as well being at increased risk of suicide. Functional allelic variations in the GR, CRH receptor, AVP1b receptor, 11β-HSD1 receptor, amino peptidase N (which controls AVP release), and P-glycoprotein genes also show an association with depression and response to antidepressant treatment.

Epigenetic changes that include DNA methylation are responsible for a reversible functional impact on gene expression caused by such things as stress, diet, and epigenetic factors. It is possible that some of this risk is attributable to the genes coding for HPA axis proteins, given a 62% heritability of basal cortisol concentrations. This is in addition to the finding that apparently healthy first-degree relatives of probands with major depressive episodes exhibit HPA dysregulation similar to that seen in affected relatives and different to the response seen in healthy controls. The failure of genome-wide association studies to identify relevant genetic polymorphisms (or for that matter any polymorphisms) associated with the HPA axis is likely attributable to the complex relationship between the environmental and genetic factors that predispose to depression.
features consistent with depression as well as impaired negative feedback regulation of the HPA axis similar to that seen in mood disorder patients.39

Glucocorticoids also have a mediating effect on neurogenesis.82 The impact of neurogenesis, neurodegeneration, and impaired neuronal networks on the precipitation and maintenance of depression has previously been demonstrated83 and are supported by findings that brain-derived neurotrophic factor (BDNF) and signaling of its receptor, TrkB, play a role in recovery from depression.84 The antidepressant response to medication may be mediated by BDNF signaling through TrkB, causing brain reorganization and neurogenesis, a process that takes time and results in a delayed response.85 Serum levels of BDNF are reduced in depressed patients compared with controls,86 and a reduction in the release of BDNF84 and 5-HT uptake in platelets is seen in depression.87 Animal models have shown that the effect of antidepressants can be simulated by injecting BDNF into the hippocampus or midbrain.88,89 However, drug treatment is ineffective when levels of BDNF or TrkB are reduced.90,91

The evidence for monoamines having a role in the pathophysiology of depression comes partly from the demonstration that symptoms of depression may be induced, in vulnerable individuals, by depleting 5-HT92 and by blocking the synthesis of norepinephrine.93 The efficacy of drugs that inhibit serotonin and noradrenaline reuptake further supports this notion. It is argued that the ability of antidepressants to increase the activity of forebrain postsynaptic 5-HT1A receptors mediates the clinical response, especially for serotonin receptor reuptake inhibitors. This is driven by desensitization of somatodendritic 5-HT1A receptors in the dorsal raphe nuclei in combination with attenuated synaptic reuptake in the forebrain. There have been a number of studies demonstrating that HPA axis dysregulation is a poor prognostic factor for depressed patients receiving serotonergic antidepressants.94 The mechanism for this is suggested by rodent studies showing that even subtle alterations in HPA axis rhythm (for instance, a flattened rhythm induced by implantation of a low-dose corticosteroid pellet) can attenuate 5-HT1A autoreceptor function95 and reduce the ability of long-term fluoxetine treatment to elevate forebrain 5-HT.96 This effect is reversed by administration of GR antagonists. Importantly, it has also been shown that GR antagonists enhance the serotonergic response to serotonin receptor reuptake inhibitors97 even in rats with a normal HPA axis rhythm.98 It has been argued that the efficacy of antidepressants may be mediated directly by their effects on the HPA axis. Animal studies showed that the tricyclic imipramine and the monoamine oxidase inhibitor phencelzine have opposing effects on the activity of the HPA axis and on expression of the GR in the hypothalamus and prefrontal cortex forebrain of adrenalectomized mice.99 Similarly, impiramine and phencelzine also have different effects on brainstem GR. Phenelzine decreased GR expression in the locus coeruleus and imipramine decreased GR expression in the dorsal raphe nuclei.100

Additionally, the role of sleep in HPA axis dysfunction and the development of depression have been explored. For example, there is an existing hypothesis that obstructive sleep apnea through repeated arousals and subsequent cortisol release leads to HPA axis activation101 and this has been linked to the development of depression.102 Further, an animal model has been applied and shown the consequences of chronically disrupted and restricted sleep on HPA axis dysfunction.103

Overall, HPA dysfunction is commonly seen in patients with depression, and although not always present in such individuals, it does have links with increased severity. Post mortem studies of patients with a history of depression who later committed suicide reveal an association with both reduced and increased MR expression in different areas of the brain as well as reduced expression in other areas. Such findings may pave the way for future studies in vivo, allowing early detection of individuals with dysregulated HPA. HPA dysfunction does not have a clear genetic basis but is believed to be attributable to complex relationships between the environmental and genetic factors.

Neuropsychological dysfunction in mood disorders and the HPA axis

Neuropsychological impairments are a common concomitant of Cushing’s syndrome104 and resolve with successful endocrinology treatment.105 Such deficits are also seen following acute or chronic exogenous administration of steroids14,106 and have been identified in patients with unipolar107 and bipolar108 mood disorders. Cognitive dysfunction has been linked to the duration of illness, number of previous manic episodes, hospitalizations, and suicide attempts.109 However, cognitive deficits do not appear to be restricted to patients in acute phases of illness, but have been found in euthymia,108 suggesting persistence into recovery and raising the possibility that these deficits may predate the emergence of symptoms.110 The deficits may be attributed to HPA axis dysregulation, which has been shown in some111,112 but not all113 studies, to be associated with neuropsychological impairment. Moreover, reduced cortisol levels and effective treatment of depression have been shown to correlate with improvement in several
domains of neuropsychological performance. The effect of cortisol on verbal memory is possibly independent of diagnosis in patients. Patients who have recovered from a major depressive episode may be especially vulnerable to the detrimental effects of subtle HPA disturbances on cognitive performance.

Cognitive deficits have been identified in patients with mood disorders and appear related to HPA dysfunction and raised cortisol levels. Although treatment tends to ameliorate such neuropsychological impairment, individuals who have recovered from a major depressive episode may be especially vulnerable to cognitive impairment secondary to small disturbances in HPA dysfunction. Such individuals would appear to have a reduced tolerance to future stress.

**Treatments that target the HPA axis**

The putative role of stress in the etiology of depression, the evidence of HPA axis dysregulation, and the negative effects of this dysregulation on the response to antidepressant therapy supports the use of drugs targeting the HPA axis as novel therapeutic strategies. There are a number of potential sites within the HPA axis that could be targeted as monotherapy approaches or as augmenting agents for traditional antidepressants.

**Cortisol synthesis inhibitors**

Aminoglutethimide attenuates the conversion of cholesterol to pregnenolone (Figure 2) and hence would be expected to reduce the synthesis of a wide range of adrenal steroids. It has shown promise in open trials of depression in combination with other drugs that affect cortisol biosynthesis.

Ketoconazole is an antifungal agent with antiguocorticoid effects; specifically, it inhibits the side chain cleavage in the conversion of cholesterol to pregnenolone and inhibits the action of 11β-hydroxylase. Efficacy in depression was suggested by case reports and by small open studies. Malison et al did not demonstrate benefit in a 6-week, double-blind, placebo-controlled trial in 16 adult patients with treatment-refractory major depressive disorder. However, a subsequent study by Wolkowitz et al reported efficacy in a double-blind trial of depressed patients who were hypercortisolemic at baseline.

Metyrapone inhibits 11β-hydroxylase and 11β-HSD2 (see Figure 2). Antidepressant properties of metyrapone have been demonstrated in small clinical trials in treatment-resistant depression with coadministration of hydrocortisone and imipramine. Jahn et al have demonstrated a beneficial effect on mood symptoms in a double-blind, randomized trial involving 63 in-patients with a DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) diagnosis of major depressive disorder. These patients were randomized to receive either metyrapone 1 g/day or placebo augmentation of the serotonergic drugs nefazodone or fluvoxamine for 3 weeks. The ADD (Antiguocorticoid augmentation of anti-Depressants in Depression) study currently being carried out by our group is a randomized, controlled trial of metyrapone augmentation of serotonergic antidepressants in 165 patients with treatment-resistant depression and will evaluate the efficacy of this cortisol synthesis inhibitor. The results of this study are not yet available.

**Glucocorticoid receptor antagonists**

The abortifacient, mifepristone, is a progesterone receptor antagonist and also a powerful glucocorticoid receptor antagonist. There have been a number of treatment studies involving the use of mifepristone for psychotic major depression, predominantly by the group based at Stanford. Initial open and small, double-blind, placebo-controlled trials in patients with psychotic depression suggested efficacy. Subsequent, larger, randomized controlled trials by the same group showed a benefit for psychotic but not mood symptoms in one trial and no benefit on primary outcome measures in a second. A further trial has shown the importance of plasma levels of mifepristone, with a benefit seen in patients whose levels were above a cut-off point. The group is conducting a further clinical trial of mifepristone in psychotic major depression using the higher (1,200 mg) dose.

Our group reported selective improvements in spatial working memory performance, verbal fluency, and spatial recognition memory following treatment with mifepristone 600 mg/day in a 3-week, double-blind, crossover design in bipolar depression. In a parallel-design replication, using spatial working memory as the primary outcome, mifepristone was associated with a sustained improvement, which was evident 7 weeks after cessation of treatment. The improvement in depressed mood seen in the first study was not confirmed in the replication study.

Mifepristone is also being assessed in ongoing trials in a number of other disorders to assess its benefits, ie, in post-traumatic stress disorder, alcoholism (for craving), cognitive impairment, depression in Gulf war veterans, and in borderline personality disorder.
Dehydroepiandrosterone and treatment of affective disorders

Dehydroepiandrosterone (DHEA) is an endogenous steroid produced in the adrenal gland. It is an intermediate in the production of the sex hormones. Open and randomized, double-blind trials of DHEA in patients with depression have shown benefits in depressive symptoms and memory performance. The efficacy of DHEA in the treatment of dysthymia as well as in human immunodeficiency virus-positive cohorts has also been demonstrated.

Dexamethasone

Open and small-scale, randomized, controlled trials have demonstrated a benefit of dexamethasone in the treatment of depressive symptoms. Dinan et al reported a significant improvement in Hamilton scores in six of ten patients in response to dexamethasone augmentation of previously ineffective standard antidepressant therapy.

Corticotrophin-releasing hormone antagonists

The selective CRH1 receptor antagonist, R121919, attenuates the endocrine stress response in rodents and was shown to reduce depression scores in a dose-escalation, open-label Phase II study in depressed patients without affecting weight or leptin levels. A reversible increase in liver enzymes in a separate Phase I study led to discontinuation of its clinical development. There has been a series of other compounds that have generated promising animal data, but a number of these have led to abandoned negative Phase II trials, eg, CP-316,311 in a recurrent depression trial, pexacertont (BMS-562,086) in a generalized anxiety disorder trial, and GS561679 in a depression study. The results of a depression trial using SSR125543, the Sanofi-Aventis compound, are not yet available. There are ongoing trials looking at the benefits of pexacertont in anxiety-related alcohol craving and of GS561679 on the human startle response in normal volunteers and in post traumatic stress disorder, and of a CRF1 antagonist in social anxiety.

The CRF2 receptor has been suggested to mediate an anxiolytic response. This, in addition to recent work elucidating the structure of the CRH1 receptor and the nature of its ligand interactions, may support the further development of novel CRH antagonists.

Vasopressin receptor antagonist

Vasopressin serves as a regulator of the HPA axis, potentiating the stimulatory effects of corticotrophin releasing hormone as well as the relative refractoriness to glucocorticoid feedback in chronic stress. It exerts its effects on the brain mainly via V1a receptors and V1b receptors which are located in the anterior pituitary, through which it mediates corticotrophin secretion. V1a receptors are abundant in the cerebral cortex, limbic system, hypothalamus, and brain stem. There are a number of antagonists of V1a, V1b, and V2 in development, particularly for the treatment of hyponatremia. The non-peptide V1b receptor antagonist, SSR149415, has demonstrated anxiolytic and antidepressant properties in animal models. However, the lack of efficacy demonstrated in clinical trials in patients with generalized anxiety disorder and depression led to discontinuation of development of the compound by Sanofi. Abbott Laboratories has made a strategic decision to discontinue a depression trial, although a study using heavy drinking days in patients with alcohol dependence as the outcome measure is still recruiting. V1a receptor antagonists being examined in Phase I trials include the Azevan Pharmaceuticals Inc compounds SRX 251 and SRX 246. Roche also has RG7314 in a Phase II trial in autism spectrum disorder.

A number of novel medications that target the HPA axis have recently been developed. Because HPA axis dysfunction is believed to be associated with a reduced response to antidepressant treatment as well as a poorer prognosis, the HPA itself has been identified as a therapeutic target. Cortisol synthesis inhibitors, glucocorticoid receptor antagonists, DHEA, dexamethasone, CRH receptor antagonists, and vasopressin receptor antagonists are medications that may in time prove beneficial in treating refractory depression. Larger studies with a greater duration of follow-up are required to determine whether these novel therapies are both safe and effective.

Outcomes measures and prediction of response

The hope that antiglucocorticoid strategies would revolutionize psychiatric treatment has not been realized. This does not necessarily mean that this approach should be discarded, rather that thought needs to be given to appropriate outcome measures and populations.

In the studies above, it appears there was some benefit of mifepristone augmentation, particularly where higher concentrations were achieved. In mifepristone studies of psychotic major depression, the psychotic symptoms may respond preferentially. The randomized controlled trial of metyrapone is promising, as are the preliminary studies with the CRH receptor antagonists, but all these findings require replication.
It is noteworthy that the bipolar mifepristone studies demonstrated a significant effect on spatial working memory, with no appreciable benefit on depressive symptoms.\textsuperscript{136,137} It could be argued that future HPA efficacy studies should focus on improving neuropsychological performance.

HPA axis dysregulation is not invariable in mood disorder patients. Studies may benefit from identifying those who are more likely to respond and hence examining efficacy in enriched samples. In the future, endocrinology and genetic measures of the HPA axis may inform individual treatment plans.

**Future perspectives**

We look forward to results of further trials targeting the HPA axis in the treatment of affective disorders with the hope of developing novel, safe, and effective treatments that overcome the negative effects of dysregulation of the HPA axis on the antidepressant response. Such strategies may deliver a rapid and sustained response, either as monotherapy agents or as augmenters of other antidepressant strategies. The roles of the infralimbic cortex, which has the mesocortical dopaminergic system as its afferent modulator,\textsuperscript{174} and iron deficiency anaemia in infancy\textsuperscript{175} in regulating behavioral and physiological responses via the HPA axis need further exploration.

**Disclosure**

The authors report no conflicts of interest in this work.

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