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Hypothalamic-pituitary-adrenal (HPA) axis functioning as predictor of antidepressant response – meta-analysis

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Highlights

- 39 studies investigated HPA functioning as a predictor of antidepressant response
- Non-responders did not differ from responders in pre-treatment CRH and ACTH
- Non-responders had higher cortisol in studies with a specific methodological profile

Abstract

Objective

Although antidepressants are effective, around 50% of depressed patients are non-responsive. At the same time, some patients show alterations in the hypothalamic-pituitary-adrenal (HPA) axis. Due to interactions with central monoaminergic systems, these may profit less from antidepressants.

Method

To determine whether non-responders and responders differed in pre-treatment HPA axis functioning, the Cochrane Library, EMBASE, MEDLINE, and PsycINFO were searched. Studies using patients with depression being treated with antidepressants, and including both a pre-treatment HPA and a post-treatment response measure were included. Standardised mean differences were calculated for meta-analysis.

Results

Thirty-nine studies were included. Non-responders and responders did not differ in pre-treatment corticotropin-releasing hormone or adrenocorticotropic hormone. Meta-regression showed non-responders had comparably higher pre-treatment cortisol in studies measuring cortisol non-invasively, not reporting sample storage, failing to control for age, and excluding patients with comorbidities.

Conclusions

Only studies with a specific methodological profile seem to be able to show that the more marked depressed patients' alterations in the HPA axis, the less likely they are to profit from antidepressants.

Keywords: antidepressant; cortisol; depression; hypothalamic-pituitary-adrenal axis; treatment response

1. **Introduction**

Antidepressants are among the most widely used first-line treatments for major depressive disorder (MDD); however, unfortunately, around 50% of patients are non-responsive to initial antidepressant

trials (Cleare et al., 2015). This raises the urgent question of which mechanisms underlie this phenomenon. One explanation is for there to exist subgroups of depressed patients, characterised by distinct pathophysiological profiles.

One of the most consistent findings in MDD is of alterations in the hypothalamic-pituitary-adrenal (HPA) axis (de Kloet et al., 2007; Rohleder et al., 2010; Stetler and Miller, 2011; Waters et al., 2015). In healthy individuals, the HPA axis is characterised by both a marked diurnal rhythm (including an increase in cortisol upon awakening; Clow et al., 2010) and by its responsivity to a variety of stimuli (e.g., psychosocial stress; Skoluda et al., 2015). It is thus important to distinguish between *basal* and post-challenge HPA measures, the latter including both *stimulation* and *suppression* of the HPA axis. Upon stimulation, arginine vasopressin (AVP) and corticotropin-releasing hormone (CRH) are secreted by the paraventricular nuclei of the hypothalamus, which in turn initiate the synthesis of adrenocorticotropic hormone (ACTH) in the anterior pituitary (Nicolaides et al., 2015). Adrenocorticotropic hormone travels through the bloodstream to release the glucocorticoid cortisol in the adrenal cortex. This cascade is terminated by a negative feedback loop, whereby cortisol passes the blood-brain-barrier and *suppresses* the release of AVP, CRH and ACTH by attaching to mineralocorticoid (MR) and glucocorticoid receptors (GR).

In MDD, there is evidence for multiple alterations along this axis, including elevated levels of CRH (Waters et al., 2015), elevated levels of ACTH and cortisol (Stetler and Miller, 2011), reduced glucocorticoid sensitivity (Rohleder et al., 2010), and MR/GR imbalance (de Kloet et al., 2007). These findings may shed light on the phenomenon of treatment non-response insofar as the HPA axis interacts with central monoaminergic systems, which in turn are targeted by antidepressants. For instance, CRH receptors are abundantly expressed in extra-hypothalamic areas, such as the raphe nuclei and the locus coeruleus, which constitute the major cell bodies of the serotonin (5-HT) and noradrenaline (NA) system, respectively (Valentino and Commons, 2005; Valentino and Van Bockstaele, 2008). Under conditions of acute stress, CRH can excite 5-HT neurons in the dorsal rape nucleus and modulate NA activity in the locus coeruleus by shifting the firing pattern from phasic to tonic (Joels and Baram, 2009). Glucocorticoids, via the MR and GR, are equally known to stimulate both the 5-HT and NA systems (de Kloet et al., 2005). Alterations in HPA functioning, as found in depressive disorders, are therefore likely to be paralleled by disturbances of this intricate interplay, which could in turn render affected individuals less likely to benefit from antidepressant treatment.

Taken together, a subgroup of depressed patients with alterations in the HPA axis may be less likely to respond to treatment with antidepressants. The aim of the present study was to find out whether non-responders could be distinguished from responders by means of HPA markers. To this end, we integrated previous studies on this topic using meta-analysis. In doing so, we provide the first comprehensive quantitative summary of this literature. We distinguished between HPA markers of central and peripheral origin, and between *basal* concentrations and concentrations obtained upon *stimulation* or *suppression* of the HPA axis and conducted separate meta-analyses for each category. An additional aim was to identify factors that contribute to study findings by using meta-regression. Based on a previous meta-analysis on the dexamethasone suppression test and antidepressant response (Ribeiro et al., 1993) and on a review on glucocorticoids as predictors of antidepressant response (Horstmann and Binder, 2011), we hypothesised that non-responders would have more marked pre-treatment HPA alterations when compared to responders. However, we hypothesised that this would only be found in studies controlling for illness severity (e.g., Juruena et al., 2009), the previous intake of psychotropic medication (Fischer et al., 2017a), and in those using a reliable (i.e., repeated or long-term) HPA measurement (e.g., Herane Vives et al., 2015).

2. Method

2.1 Search strategy

Records were identified by searching the Cochrane Library, EMBASE, MEDLINE, and PsycINFO databases from the first available year until October 2015. Key words and subject headings were combined in accordance with the thesaurus of each database. The search string consisted of three components: 1) “HPA axis” and synonyms, including its components (e.g., “cortisol”), 2) “depressive disorder”, including synonyms, and 3) “antidepressant” and synonyms, including the most widely prescribed antidepressants (e.g., “citalopram”). All searches were restricted to research in humans. Only studies published in English, German, Dutch, French, Italian, or Spanish were to be included.

2.2 Screening and selection procedure

Records were screened regarding the following inclusionary criteria: 1) adult patients suffering from any depressive disorder (i.e., MDD, persistent depressive disorder) diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), the International Classification of Diseases (ICD), or

Research Diagnostic Criteria (RDC), 2) any kind of pre-treatment assessment of AVP, GR levels, CRH, ACTH, or cortisol, and 3) treatment including at least four weeks of continuous administration of monoamine oxidase (MAO) inhibitors, tri- or tetracyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), noradrenaline reuptake inhibitors (NRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), noradrenaline-dopamine reuptake inhibitors (NDRIs), or serotonin-noradrenalin-dopamine reuptake inhibitors (SNDRIs), and 4) standardised post-treatment symptom measure with a reported cut-off value dividing patients into non-responders and responders. Studies including bipolar patients were excluded, unless results were reported separately for unipolar and bipolar patients allowing for data to be extracted selectively. Comorbidity with somatic diseases, mental disorders, intake of medication upon study entry, and intake of medication *pro re nata* during the study were allowed, but recorded for meta-regression (see below). Studies delivering a mixture of different antidepressants or a combination of psychological and pharmacotherapy were included, but again, this was noted for subgroup analyses. Similarly, studies using response (e.g., a HAMD decrease of ≥ 50%) and/or remission (e.g., a HAMD score < 10) criteria were included and first analysed together and then separately. The search was complemented with a manual review of reference lists.

2.3 Data extraction

For each study, information was collected about the first author, its year of publication, the number of patients for which data were available for extraction, diagnostic procedures, diagnosis including subtype of depressive disorder, other sample characteristics (e.g., symptom severity), eligibility criteria (e.g., medication use upon study entry), pre-treatment assessment of HPA functioning, blinding to HPA-related results, antidepressant treatment characteristics, response rates, and statistical analyses. Risk of bias was assessed by means of a modified version of a quality assessment tool that was used in two previous meta-analyses on cortisol as a predictor of psychological therapy response (Fischer and Cleare, 2017; Fischer et al., 2017b). Seven items were scored on a three-point scale (0-2). These included the number of used eligibility criteria, the adequacy of diagnostic procedures, the quality of the HPA axis assessment, the adequacy of the antidepressant treatment, the validity of the outcome assessment, the blinding procedure, and the use of relevant confounders in statistical analyses. The maximum attainable quality score was 14.

2.4 Statistical analysis

To quantify the differences between non-responders and responders in HPA assessments at baseline, standardised mean differences were calculated based on mean values and standard deviations or based on frequency tables. This was done in accordance with the procedures outlined by Lipsey and Wilson (2001) and Borenstein et al. (2009). Whenever insufficient statistical parameters were reported, the authors were contacted. If it was not possible to gather additional data, the study was excluded. Hedge's *g* was calculated from standardised mean differences to correct for small sample bias. Studies were weighed based on the inverse variance method (Borenstein et al., 2009; Lipsey and Wilson, 2001). Separate analyses were conducted for each HPA marker, and within individual markers for *basal*, *stimulation*, and *suppression* values. Aggregated effect sizes (ES) including a 95% CI were calculated using SPSS 22 and the macros developed by David B. Wilson (http://mason.gmu.edu/~dwilsonb/ma.html) Random rather than fixed effects meta-analyses were considered appropriate.

Heterogeneity was indicated by means of Q and I^2 statistics. Subgroup analyses were undertaken to study the effects of categorical variables, such as specific subtypes of depression (atypical, melancholic, persistent), different types of medication (MAO inhibitors, tri- or tetracyclic antidepressants, SSRIs, NRIs, SNRIs, NDRIs, SNDRIs), different challenges and different responder criteria on our results. Random effects meta-regressions were calculated to explore dichotomous and continuous sources of heterogeneity, but only when at least ten studies were available. Candidate effect modifiers were sex distribution (percentage of female patients; see e.g., Binder et al., 2009), symptom severity upon study entry (i.e., Hamilton Rating Scale for Depression score), the intake of psychotropic medication upon study entry (user percentage), single time point vs. aggregated HPA assessments, non-invasive (i.e., urine or saliva) vs. invasive (i.e., blood) measurement of cortisol, use of a naturalistic vs. standardised treatment approach, and the duration of treatment (number of weeks). In addition, each item of the quality assessment tool was tested in terms of being a potential predictor. Whenever at least ten studies were available, publication bias was to be examined by visual inspection of funnel plots and a trim and fill procedure (Duval and Tweedie, 2000).

3. Results

3.1 Search process

The search yielded 28,808 records, of which 511 were considered potentially relevant based on their title or abstract. Of these, 472 were excluded because they were not original research, were conducted in healthy people, included depressed patients with bipolar disorder, did not contain HPA measures, did not administer antidepressants, administered antidepressants for less than four weeks, used augmentation strategies, were retrospective in nature (e.g., cross-sectional comparison of treatment resistant patients vs. healthy controls), or did not divide patients into non-responders vs. responders based on a standardised symptom measure. It was not possible to obtain the necessary statistical parameters of seven studies. In total, 39 studies were eligible for data extraction.

3.2 Characteristics of included studies

Table 2 shows the main characteristics of the 39 included studies (see supplement 1 for a complete list of references). The first included study dated back to 1984 and the last one was published in 2015. The number of patients for which relevant data were available ranged from 5 to 290. Studies were weighted towards female participants, the average proportion being 63%. Most studies (n=26; 67%) did not indicate to which subtype of depression their patients belonged; three (8%) stated that their patients were non-psychotic and one indicated that all patients were non-atypical; the remainder used mixed subtypes or were confined to one specific subtype. More than half of the studies (n=25, 64%) used a severity cut-off as an inclusionary criterion (e.g., HAMD score ≥ 18). Nearly three quarters (74%) excluded at least some medical conditions, 64% excluded comorbidity with other mental disorders to some extent, and 69% excluded or washed out psychotropic drugs upon study entry. Nearly all studies published in the 1980s used the dexamethasone suppression test (DST; Carroll, 1982) to challenge the HPA axis and detect alterations in ACTH and cortisol, whereas studies conducted in the 1990s and 2000s used a broad range of central and peripheral HPA parameters, and often reported both *basal* and post-challenge values. Amitriptyline was the most widely used antidepressant (11 studies, 28%), followed by citalopram/escitalopram and fluoxetine (both used in 6 studies, 15%). The majority of studies (n=27; 69%) used the Hamilton Rating Scale for Depression (HAMD) with a 50% minimum decrease in depressive symptoms as responder criterion. The average response rate was 56%, ranging from 31% to 91%. Nine studies (23%) used HAMD cut-off values as remitter criterion, and the average remission rate was 66% (range: 45%-91%). Quality ratings ranged from 2 to 10 (out of a maximum of 14), with an average of 6 points.

- Insert Table 1 here –

3.3 Central predictors of treatment response

In total, 11 studies looked at HPA parameters of central origin: AVP, CRH, and ACTH. As illustrated in Figure 1 (forest plot), non-responders tended to have lower initial concentrations of all central HPA markers when compared to responders (except for *suppressed* ACTH). However, meta-analysis, conducted for each parameter separately, did not find this to be significant: The one study measuring *basal* AVP did not find a difference between non-responders and responders to treatment; the same was true regarding *basal* CRH as measured in cerebrospinal fluid (n=2, mean ES=0.04, 95% CI [-0.79, 0.87]); Z=0.09, p=0.927), *basal* ACTH (n=3, mean ES=0.16, 95% CI [-0.07, 0.39]; Z=1.38, p=0.168), and *stimulated* ACTH using the dexamethasone/CRH (Holsboer et al., 1987), metyrapone, or T3/TRH test (n=6, mean ES=0.11, 95% CI [-0.21, 0.42]; Z=0.66, p=0.510). Similarly, ACTH concentrations after *suppression* with dexamethasone were not linked with treatment response (n=3, mean ES=-0.14, 95% CI [-0.87, 0.60]; Z=-0.36, p=0.716).

-Insert Figure 1 here-

The Q and I^2 statistics indicated low heterogeneity among studies measuring *basal* (Q=0.66, p=0.721, I^2=0%) or *stimulated* ACTH (Q=4.12, p=0.533, I^2=0%), and moderate to high heterogeneity in those measuring *basal* CRH (Q=1.87, p=0.171, I^2=47%) or *suppressed* ACTH (Q=4.36, p=0.113, I^2=54%). As noted above, there was rarely ever any information on which subtypes of depression were represented in the samples, which meant that diagnostic subgroup analyses were not feasible. Subgroup analyses for different pharmacological compounds were possible, but did not alter our findings, and neither did subgroup analyses for specific challenges or for studies using responder versus remitter criteria (data not shown). Due to the low number of studies using central HPA markers, it was not possible to undertake meta-regression.

3.4 Peripheral predictors of treatment response

A total of 36 studies measured HPA functioning via peripheral markers, that is, CBG (one study only) and cortisol. As can be seen in Figure 2 (forest plot), non-responders tended to have higher initial

concentrations of both peripheral HPA markers when compared to responders. However, meta-analysis, conducted for each parameter separately, again found this was not a significant difference. The only exception was the one study measuring *basal* CBG levels, which found significantly higher values in non-responders when compared to responders. *Basal* cortisol concentrations did not differ across the two groups (n=15, mean ES=-0.11, 95% CI [-0.30, 0.09]), Z=-1.09, p=0.277), and neither did *stimulated* (n=10, mean ES=-0.15, 95% CI [-0.50, 0.19]; Z=-0.86, p=0.392) or *suppressed* values (n=19, mean ES=-0.15, 95% CI [-0.41, 0.12]; Z=-1.08, p=0.279), the former including the dexamethasone/CRH, buspirone, bupropion, d-fenfluramine, and T3/TRH tests, and the latter including the dexamethasone and prednisolone suppression tests.

-Insert Figure 2 here-

Heterogeneity was low in studies using *basal* cortisol (Q=20.94, p=0.103, I^2=33%) but moderate to high in studies using *stimulated* (Q=17.19, p=0.046, I^2=48%) or *suppressed* cortisol (Q=40.58, p=0.002, I^2=56%). As before, the investigation of diagnostic subgroups to explore sources of heterogeneity was halted due to missing information. When repeating meta-analyses within particular subgroups of antidepressant compounds, findings revealed that patients with higher *basal* cortisol concentrations responded significantly less well to venlafaxine (n=2, mean ES=-0.65, 95% CI [-1.16, -0.15]; Z=-2.53, p=0.011). By contrast, subgroup analyses for specific challenges or for different responder criteria did not yield any significant findings (data not shown).

Meta-regression revealed that studies measuring cortisol in urine or saliva (β=-0.62, p=0.004), not declaring how they stored samples (β=-0.61, p=0.007) and those not statistically controlling for age (β=-0.54, p=0.022) were more likely to find that non-responders had higher *basal* cortisol values when compared to responders. In addition, those who excluded patients with any comorbid somatic (β=-0.49, p=0.015) or mental (β=-0.59, p=0.002) illness were more likely to find higher cortisol values upon *suppression* in non-responders when compared to responders. No other significant effect modifiers were identified (data not shown).

4. Discussion

This meta-analysis investigated whether HPA axis functioning predicts antidepressant treatment response in depressed patients. We report two main findings: First, non-responders and responders did not differ in any HPA markers of central origin, that is, AVP, CRH, or ACTH. Second, the same seemed to be true of cortisol, the main peripheral HPA marker. However, meta-regression revealed that studies measuring cortisol in urine or saliva, those not reporting sample storage conditions, those failing to statistically control for patients' age, and those excluding patients with comorbidity were able to demonstrate that non-responders had significantly higher pre-treatment cortisol levels when compared to responders.

A number of factors may account for the finding that neither AVP, nor CRH, or ACTH differed between non-responders and responders to antidepressant treatment, despite close interactions of the HPA and monoaminergic systems (Valentino and Commons, 2005; Valentino and Van Bockstaele, 2008). For instance, it is important to note that *basal* levels of these parameters are usually determined by means of single time point measurements (e.g., blood sampling at 8 am). Indeed, all of the studies included here conformed to this procedure. Unfortunately, the reliability of this approach is limited by evidence showing great intra-individual variability of HPA markers due to state-like moderators, such as time of day or week-day (Skoluda et al., 2016). Another explanation for our null-findings could be the confounding of results by the invasive sampling methods used to obtain AVP, CRH, and ACTH (i.e., lumbar puncture). In favour of this, Weckesser et al. (2014) in a recent review showed that venepuncture is capable of activating the HPA axis in a substantial proportion of research participants. An unequal distribution of such subjects across studies may therefore have contributed to conflicting study results. Finally, the low number of studies using central HPA markers may have rendered it impossible to detect any significant group differences in central HPA markers in the first place.

By contrast, we found *basal* cortisol to discriminate between non-responders and responders to antidepressants. However, this applied only to those studies that measured cortisol non-invasively, that is, in urine and saliva instead of blood. More specifically, non-responders had higher pre-treatment concentrations when compared to responders, which is in line with studies contrasting severely treatment-resistant patients with unipolar depression to healthy controls (Markopoulou et al., under revision). This means that patients suffering from hypercortisolaemia may overlap with those not achieving a sufficient clinical response. It is difficult to interpret the fact that confining our analysis to

studies not reporting sample storage conditions was also linked with positive findings. One explanation could be that authors choosing saliva sampling were less likely to explicitly describe sample handling, since saliva is relatively robust to the influence of environmental conditions (e.g., temperature). Plasma or serum samples, by contrast, require immediate action (e.g., centrifugation), which needs to be reported. Finally, studies failing to include age as a covariate in their statistical analyses were more likely to find significant group differences. One way to make sense of this is that very old patients have both higher cortisol levels (Miller et al., 2016; Van Cauter et al., 1996) and lower response rates to antidepressants (Cleare et al., 2015). Taken together, this suggests some of the positive results in the literature to be inflated by unadjusted statistical analysis.

Cortisol after *suppression* with dexamethasone or prednisolone also appeared to be higher in non-responders to treatment with antidepressants; however only in studies which a priori excluded patients with any somatic illness influencing endocrine systems or comorbidity with other major metal disorders. Failure to suppress cortisol secretion after administration of synthetic analogues may be indicative of attenuated negative feedback sensitivity of the HPA axis (Carroll, 1982). This finding concurs with earlier studies contrasting severely treatment-resistant patients with healthy controls and finding that the former retained higher cortisol concentrations upon *suppression* (Juruena et al., 2013). It is not surprising that this only applied to studies without any major comorbidity, seeing that substance abuse, schizophrenia, and eating disorders are all paralleled by HPA alterations (Bradley and Dinan, 2010; Chrousos, 2009). Including patients with additional illnesses may therefore have distorted cortisol values. More importantly, these illnesses themselves and/or additional medication may have interacted with patients' response to dexamethasone or prednisolone. Thus, in this case, the higher quality studies did show higher post-suppression cortisol levels were associated with a poorer response to antidepressants.

The present meta-analysis offers a number of strengths. It is the first quantitative summary of the literature on HPA functioning as a predictor of antidepressant treatment response. As such, it offers insight on whether one of the most frequently measured biological systems in depression is involved in the phenomenon of treatment-resistance, which affects around 50% of patients to some degree. Another strength is that the included studies are remarkably homogenous in choosing a minimum of a 50% decrease in HAMD scores as responder criterion. Finally, meta-regression allowed to identify factors that need to be considered by future research in this area. Nevertheless, a number of limitations should

be mentioned. First, our search yielded very few studies investigating central HPA markers as predictors of antidepressant treatment response. As a result of this, the null-findings of these particular meta-analyses need to be interpreted with caution. Second, it is a frequent finding that patients with melancholic depression are characterised by hypercortisolaemia, while patients with atypical symptoms exhibit hypocortisolaemia (Chrousos, 2009). Unfortunately, only a handful of studies reported whether they conflated diagnostic subtypes of depression, which prevented us from investigating whether our findings are exclusive to a specific group of patients. Similarly, patients with psychotic symptoms show greater degrees of hypercortisolaemia, and few studies explicitly comment on the proportion of patients with such symptoms. Third, there was a lack of information on whether patients were affected by early life or chronic stress. Again, this rendered it impossible to examine whether specific subgroups of patients, namely those with a stress-related aetiology (Heim et al., 2008), are particularly likely not to profit from treatment with antidepressants, or to have different HPA axis profiles.

Taken together, this meta-analysis shows that it highly depends on the methodological quality of a study whether it is able to show that the more marked depressed patients' hypercortisolaemia, the less likely they are to achieve a significant response to antidepressants. Studies employing *basal* HPA assessments are well-advised to use non-invasive HPA markers whenever possible. Promising new biomarkers may include hair cortisol, which allows for an estimate of long-term secretion over the course of several months (Stalder and Kirschbaum, 2012), and potentially fingernail cortisol, measuring periods of several weeks (Izawa et al., 2015). In addition, it seems sensible for studies interested in post-challenge HPA markers to select patients that are unaffected by any major somatic or mental illness except MDD. We also hope that our findings will prompt further research to add to the scant body of literature on central HPA markers and treatment response, and to explore the role of symptomatic and aetiological subtypes of depression. This may aid the ultimate goal of identifying patients that are at risk of not responding to fist-line treatments and might require alternative or adjuvant therapies.

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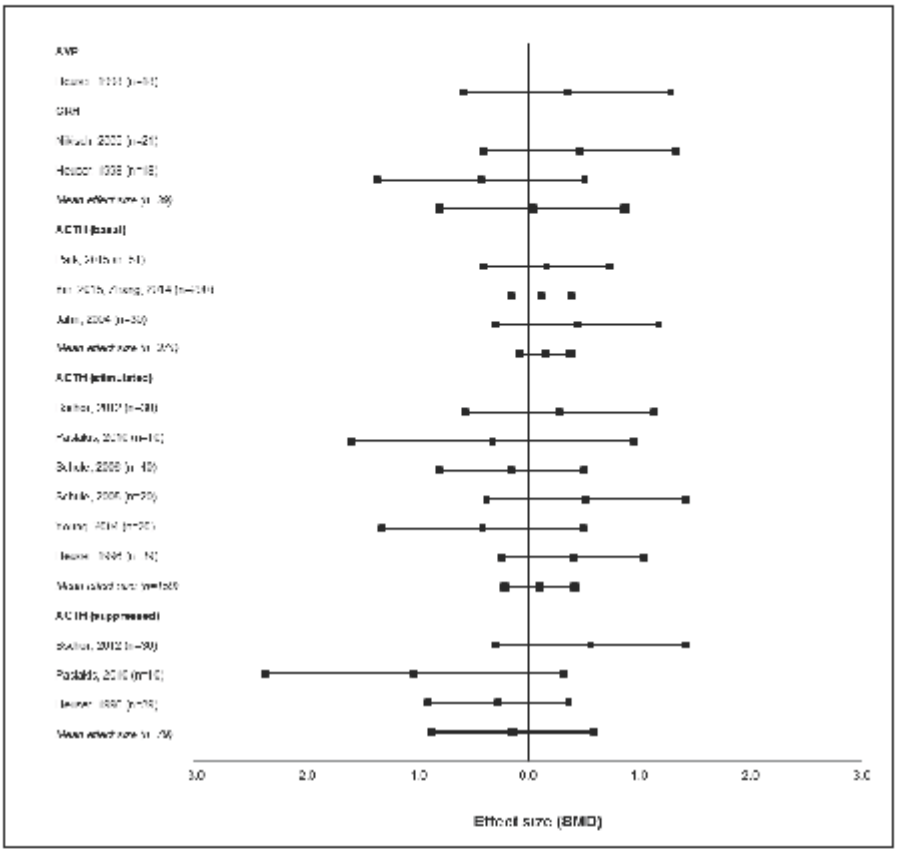
Figure 1 Forest plot of central HPA predictors of antidepressant response; individual effect sizes are reported as standardised mean differences (SMD) between non-responders and responders and 95% confidence intervals (CI), while mean effect sizes are reported as Hedge's *g*; negative effect sizes indicate that non-responders had *higher* pre-treatment concentrations of the respective parameter when compared to responders; positive effect sizes indicate that non-responders had *lower* pre-treatment concentrations of the respective parameter when compared to responders; an increase in ACTH upon stimulation (e.g., with exogenous CRH) is generally considered adaptive, whereas a failure to suppress ACTH secretion (e.g., after dexamethasone administration) is considered maladaptive. AVP = arginine vasopressin; CRH = corticotropin-releasing hormone; ACTH = adrenocorticotropic hormone; HPA = hypothalamic-pituitary-adrenal

Figure 2 Forest plot of peripheral HPA predictors of antidepressant response; individual effect sizes are reported as standardised mean differences (SMD) between non-responders and responders and 95% confidence intervals (CI), while mean effect sizes are reported as Hedge's *g*; negative effect sizes indicate that non-responders had *higher* pre-treatment concentrations of the respective parameter when compared to responders; positive effect sizes indicate that non-responders had *lower* pre-treatment concentrations of the respective parameter when compared to responders; an increase in cortisol upon stimulation (e.g., with exogenous CRH) is generally considered adaptive, whereas a failure to suppress cortisol (e.g., after dexamethasone administration) is considered maladaptive. CBG = corticosteroid binding globulin; CRH = corticotropin-releasing hormone; HPA = hypothalamic-pituitary-adrenal



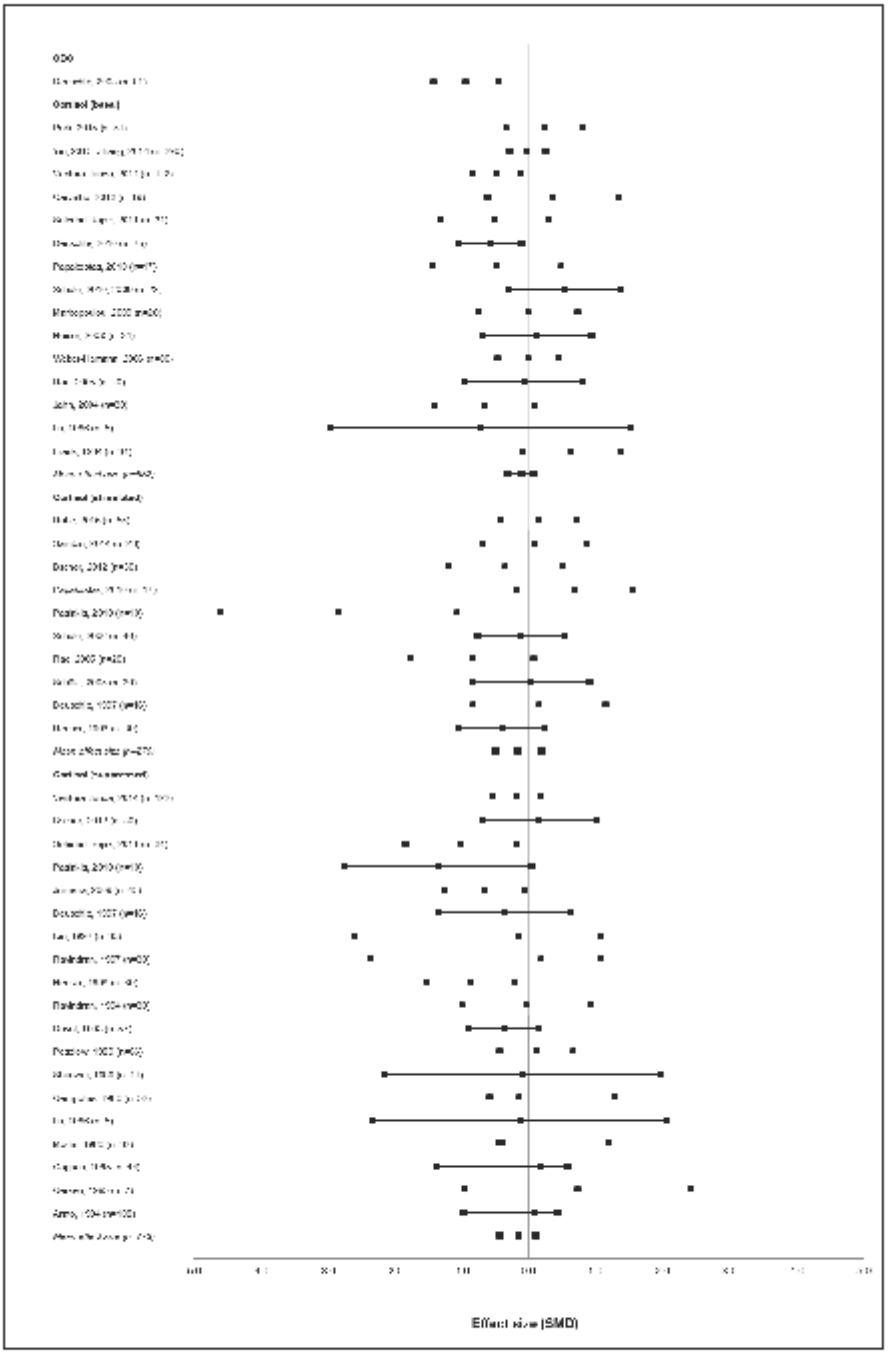


Table 1 Characteristics of included studies on hypothalamic-pituitary-adrenal (HPA) functioning in depressed non-responders vs. responders to antidepressant treatment

No.	Study	Sample (incl. extracted sample size)	HPA measure	Antidepressant	Response rate	Quality rating
1	Park, 2015	N=51 (82% female) Inclusionary criteria: MDD according to the SCID Exclusionary criteria: abnormal laboratory tests, psychotic features, suicidal ideation, treatment with antidepressant or anti-anxiety drugs within 1 month	Basal ACTH, basal cortisol (plasma)	Escitalopram	63% (HAMD decrease of ≥ 50% or HAMD score < 10)	6/14
2	Ruhe, 2015	N=55 (total sample: 66% female) Inclusionary criteria: MDD according to the SCID, HAMD score > 18 Exclusionary criteria: neurological impairments, primary	CAR (saliva)	Paroxetine	31% (HAMD decrease of ≥ 50%)	6/14

		substance abuse, bipolar disorder, psychotic features, severe suicidal ideation, primary anxiety disorder, pregnancy, antidepressant intake within 1 month, > 1 antidepressant for present episode, drugs affecting HPA functioning				
3	Yin, 2015, Zhang, 2014	N=290 (51% female) Inclusionary criteria: MDD according to the DSM-IV, HAMD score > 18 Exclusionary criteria: major medical disorders, abnormal laboratory tests, other mental disorders, pregnancy, antidepressant intake within 2 weeks	Basal ACTH, basal cortisol (blood)	Citalopram, fluoxetine, paroxetine, sertraline	76% (HAMD decrease of ≥ 50%)	8/14

		(fluoxetine: 1 month), history of ECT				
4	Sarubin, 2014	N=28 (39% female) Inclusionary criteria: MDE according to the SCID Exclusionary criteria: somatic or mental illnesses, previous non-response to escitalopram or intolerance	Cortisol after DEX/CRH test (blood)	Escitalopram	64% (HAMD decrease of ≥ 50%)	7/14
5	Ventura-Junca, 2014	N=122 (total sample: 97% female) Inclusionary criteria: MDD according to the MINI, HAMD score ≥ 15 Exclusionary criteria: medical or neurological illnesses, infections, abnormal thyroid function, hypertension, current substance abuse or comorbid mental	Basal cortisol, cortisol after DST (saliva)	Fluoxetine	55% (HAMD decrease of ≥ 50%)	8/14

		disorders, pregnancy, breastfeeding, medication intake within 2 months, history of treatment-resistance				
6	Carvalho, 2013	N=19 (74% female) Inclusionary criteria: primary affective disorder according to the ICD-10, HAMD score ≥ 16, history of treatment-resistance Exclusionary criteria: significant physical illness, alcohol dependence, pregnancy, lactation, heavy smoking, drugs affecting endocrine or immune functioning within 1 month, switch in medication within 2 weeks, hypersensitivity to corticosteroid use	Basal cortisol (plasma)	Specialist inpatient treatment	32% (HAMD decrease of ≥ 50%)	3/14

7	Bschor, 2012	N=30 (80% female) Inclusionary criteria: MDD according to the SCID, HAMD score ≥ 15 Exclusionary criteria: somatic conditions influencing mineralo- or glucocorticoid functioning, organic brain disease, alcohol abuse or dependency, schizophrenia or schizoaffective disorder, bipolar disorder, pregnancy, lactation, intake of psychotropic drugs within 1 week (except diazepam)	ACTH after DST, ACTH after DEX/CRH test, cortisol after DST, cortisol after DEX/CRH test (plasma)	Citalopram	77% (HAMD decrease of ≥ 50%)	8/14
8	Soledad Rojas, 2011	N=34 (71% female) Inclusionary criteria: MDD according to the MINI Exclusionary criteria: infections, abnormal	Basal cortisol, cortisol after DST (saliva)	Venlafaxine	77% (HAMD decrease of ≥ 50%)	8/14

		thyroid function, hypertension, other mental illnesses, pregnancy, nursing, oral contraceptives, hormone replacement, antidepressants or mood stabilisers within 1 month				
9	Deuschle, 2010	N=75 (65% female) Inclusionary criteria: depression according to the DSM-IV, HAMD score ≥ 18 Exclusionary criteria: current substance abuse, lifetime schizophrenia or bipolar disorder, dieting, antidiabetic drugs, lipid-lowering drugs, fluoxetine or injectable antipsychotic drugs, psychotropics within 1 week	Basal cortisol (saliva)	Mirtazapine, venlafaxine	45% (HAMD score ≤ 7)	4/14

10	Papakostas, 2010	N=17 (59% female) Inclusionary criteria: MDD according to the SCID, HAMD score ≥ 15, using effective contraception Exclusionary criteria: unstable physical disorder, lifetime history of organic mental disorder, psychotic disorder, or mania, psychotic features, significant risk of suicide, pregnancy, breastfeeding, oral steroids or steroid inhibitors, antidepressants, adverse reaction to study drug, history of treatment-resistance	Basal cortisol, cortisol after buspirone challenge (saliva)	Citalopram	47% (HAMD decrease of ≥ 50%)	6/14
11	Paslakis, 2010	N=10 (0% female) Inclusionary criteria: MDD according to the DSM-IV, melancholic	ACTH after DST, ACTH after DEX/CRH test, cortisol	Fluoxetine	60% (HAMD decrease of ≥ 10 points)	7/14

		subtype, HAMD score ≥ 18 Exclusionary criteria: relevant physical illness, other mental disorders, psychotropics within 1 week	after DST, cortisol after DEX/CRH test (blood)			
12	Schüle, 2010, 2009	N=23 (83% female) Inclusionary criteria: MDE according to the SCID, melancholic subtype, HAMD score ≥ 18 Exclusionary criteria: major medical illness, bipolar disorder, other mental disorders, pregnancy, oral contraceptives, angiotensin-converting enzyme inhibitors, oral steroids, hormonal replacement, psychotropic drugs	Basal cortisol (plasma)	Mirtazapine	52% (HAMD decrease of ≥ 50%)	10/14

		within 5 days (except chloralhydrate)				
13	Juruena, 2009	N=45 (82% female) Inclusionary criteria: MDD according to the SCID, history of treatment-resistance Exclusionary criteria: significant physical illness, viral illness within 2 weeks, alcohol dependence, organic cause for MDD, psychotic symptoms unrelated to the MDE, bipolar disorder, heavy smoking, pregnancy, lactation, steroid use, hypersensitivity to corticosteroids, switch in medication regimen within 7 days	Cortisol after prednisolone test (saliva)	Specialist inpatient treatment	53% (HAMD decrease of ≥ 50%)	5/14
14	Markopoulou, 2009	N=28 (79% female) Inclusionary criteria: MDD according to the	Basal cortisol (plasma)	Specialist inpatient treatment	50% (HAMD decrease of ≥ 50%)	5/14

		SCID, history of treatment-resistance Exclusionary criteria: organic cause for MDD, excess alcohol use				
15	Heiser, 2008	N=24 (38% female) Inclusionary criteria: MDD according to the SCID Exclusionary criteria: infectious, autoimmune, allergic, neoplastic, or endocrine diseases, heart or brain infarct or surgery within 3 months, drug abuse, other mental disorders, pregnancy, antipsychotics within 6 months, antidepressants within 6 weeks	Basal cortisol (plasma)	Amitriptyline	58% (HAMD and MADRS decrease of ≥ 50%)	8/14
16	Schüle, 2006	N=40 (58% female)	ACTH after DEX/CRH	Mirtazapine, reboxetine	65%	9/14

		Inclusionary criteria: MDE according to the SCID, HAMD score ≥ 18 Exclusionary criteria: major medical illnesses, bipolar disorder, other mental disorders, pregnancy, oral contraceptives, psychotropic drugs within 5 days (except chloralhydrate)	test (plasma), cortisol after DEX/CRH test (serum)		(HAMD decrease of ≥ 50%)	
17	Weber-Hamann, 2006	N=80 (69% female) Inclusionary criteria: MDE according to the DSM-IV, HAMD score ≥ 18 Exclusionary criteria: current substance-related disorders, lifetime schizophrenia, bipolar disorder, atypical features, dieting, antidiabetic drugs, lipid-lowering	Basal cortisol (saliva)	Amitriptyline, paroxetine	64% (HAMD decrease of ≥ 50% or HAMD score < 7)	5/14

		drugs, psychotropics within 1 week				
18	Nikisch, 2005	N=21 (57% female) Inclusionary criteria: MDD according to the DSM-IV Exclusionary criteria: serious medical illnesses, ongoing lithium treatment, drugs that could interfere with central nervous amine metabolites within 1 week, ECT within 4 weeks, previous participation in clinical trial (citalopram)	CRH (CSF)	Citalopram	52% (HAMD decrease of ≥ 50%)	5/14
19	Rao, 2005	N=20 (50% female) Inclusionary criteria: MDD according to the SCID, HAMD score ≥ 15 Exclusionary criteria: neurological condition, medical	Basal cortisol, cortisol after bupropion challenge (8h nocturnal urine)	Bupropion	55% (HAMD decrease of ≥ 50%)	7/14

		illness, substance use disorder within 6 months, psychotic disorder, bipolar disorder, active suicidal ideation or recent suicide attempt, primary anxiety disorder, anorexia/bulimia nervosa, history of sleep disorders, pregnancy, psychotropics within 1 month (2 months for fluoxetine), prior use of bupropion				
20	Schüle, 2005	N=20 (60% female) Inclusionary criteria: MDE according to the DSM-IV, HAMD score ≥ 18 Exclusionary criteria: major medical illnesses, bipolar disorder, other mental disorders, pregnancy, oral contraceptives,	ACTH after TRH test, ACTH after T3/TRH test (plasma), cortisol after TRH test, cortisol after T3/TRH test (serum)	Sertraline	50% (HAMD decrease of ≥ 50%)	7/14

		psychotropic drugs within 5 days (except chloralhydrate)				
21	Jahn, 2004	N=30 (53% female) Inclusionary criteria: MDD according to the DSM-IV, HAMD score ≥ 18, using effective contraception Exclusionary criteria: serious medical conditions, drug abuse, other axis I disorders, pregnancy, nursing, medication within 5 days (except anti-hypertensives)	Basal ACTH, basal cortisol (plasma)	Nefazodone, fluvoxamine	33% (HAMD decrease of ≥ 50%)	7/14
22	Young, 2004	N=20 (100% female) Inclusionary criteria: MDD according to the SCID, HAMD score ≥ 20, premenopausal Exclusionary criteria: other axis I disorders (except anxiety	ACTH after metyrapone challenge (blood)	Fluoxetine	40% (HAMD decrease of ≥ 50%)	7/14

		disorders), failed trial of fluoxetine within 1 year				
23	Deuschle, 2003	N=81 (70% female) Inclusionary criteria: MDE according to the DSM-IV, HAMD score ≥ 18 Exclusionary criteria: lifetime schizophrenia or bipolar disorder, current substance-related disorder, psychotropic medication within 6 days	CBG (serum)	Amitriptyline, paroxetine	68% (HAMD decrease of ≥ 50%)	4/14
24	Heuser, 1998	N=18 (total sample: 70% female) Inclusionary criteria: MDE according to the DSM-III-R Exclusionary criteria: mood-incongruent psychotic features, previous intake of fluoxetine,	AVP, CRH (CSF)	Amitriptyline	50% (HAMD decrease of ≥ 50%)	4/14

		psychotropics within 5 days				
25	Deuschle, 1997	N=16 (sex distribution not reported) Inclusionary criteria: MDE according to the DSM-III-R, HAMD score ≥ 18 Exclusionary criteria: physical illness, antipsychotics within 6 months	Cortisol after DST, cortisol after DEX/CRH (blood)	Doxepin	56% (HAMD decrease of ≥ 50%)	5/14
26	Kin, 1997	N=35 (sex distribution not reported) Inclusionary criteria: MDD according to the DSM-III-R, HAMD score ≥ 18 Exclusionary criteria: psychotropics within 7 days	Cortisol after DST (plasma)	Nortriptyline	31% (HAMD decrease of ≥ 50%)	3/14

27	Ravindran, 1997	N=30 (63% female) Inclusionary criteria: MDD according to RDC and the DSM-III Exclusionary criteria: significant physical illness, psychotropic drugs within 4 days	Cortisol after DST (plasma)	Imipramine	50% (HAMD decrease of ≥ 50% and HAMD score < 10)	2/14
28	Heuser, 1996	N=39 (82% female) Inclusionary criteria: MDE according to the DSM-III-R, HAMD score ≥ 18 Exclusionary criteria: major medical illness, major mental disorders, slow-release antipsychotics, benzodiazepines, barbiturates, lithium, or carbamazepine for > 6 months, psychotropics within 5 days	ACTH after DST, ACTH after DEX/CRH test, cortisol after DST, cortisol after DEX/CRH test (plasma)	Amitriptyline	54% (HAMD decrease of ≥ 50% or HAMD score < 10)	7/14

29	Ravindran, 1994	N=30 (60% female) Inclusionary criteria: primary dysthymia according to the DSM-III-R Exclusionary criteria: significant medical illness, other mental disorders, psychotropics within 1 week	Cortisol after DST (plasma)	Fluoxetine	83% (HAMD decrease of ≥ 50% and HAMD score ≤ 7)	5/14
30	Duval, 1993	N=57 (60% female) Inclusionary criteria: MDD according to the DSM-III-R Exclusionary criteria: bipolar disorder	Cortisol after DST (plasma)	Amitriptyline, fluoxetine, toloxatone	46% (HAMD score < 8)	5/14
31	Peselow, 1989	N=66 (35%female) Inclusionary criteria: MDD according to the DSM-III, HAMD score ≥ 18 Exclusionary criteria: active medical illness,	Cortisol after DST (plasma)	Imipramine, paroxetine	58% (HAMD decrease of ≥ 50% and BDI ≥ 50%, or CGI ≥ 2)	6/14

		endocrinopathy, substance abuse				
32	Shunwei Li, 1989	N=11 (64% female) Inclusionary criteria: primary endogenous MDD according to RDC Exclusionary criteria: none reported	Cortisol after DST (plasma)	Amitriptyline, desipramine, imipramine, nortriptyline, phenelzine	91% (HAMD decrease of ≥ 50% and HAMD score < 10)	3/14
33	Georgotas, 1986	N=52 (total sample: 58% female) Inclusionary criteria: MDD according to RDC, HAMD score ≥ 16 Exclusionary criteria: serious neurological disorders, dementia, drug or alcohol dependence, active suicidality, mental retardation, other major mental disorders, urinary retention, glaucoma, antipsychotics, lithium,	Cortisol after DST (plasma)	Nortriptyline, phenelzine	58% (HAMD score ≤ 10)	7/14

		carbamazepine, MAO inhibitors within 1 year, drugs influencing dexamethasone pharmacokinetics, antidepressants within 1 week, super-sensitivity to antidepressants				
34	Lu, 1986	N=5 (60% female) Inclusionary criteria: primary endogenous MDD according to the DSM-III, HAMD score ≥ 18 Exclusionary criteria: abnormal physical or laboratory testing, body weight within 20% of ideal weight, lifetime slow-release antipsychotics, ECT, insulin shock therapy, or corticosteroids, antipsychotics or antidepressants within 1 month, any	Basal cortisol, cortisol after DST (plasma)	Imipramine	80% (HAMD score < 14)	6/14

		medication within 1 week				
35	Modai, 1986	N=32 (total sample: 63% female) Inclusionary criteria: MDE according to the DSM-III Exclusionary criteria: physical illness interfering with the DST	Cortisol after DST (blood)	Amitriptyline, chlorimipramine, phenelzine	63% (BDI decrease of > 10 points)	3/14
36	Coppen, 1985	N=44 (59% female) Inclusionary criteria: MDD according to RDC, HAMD score ≥ 16 Exclusionary criteria: drugs influencing dexamethasone kinetics	Cortisol after DST (plasma)	Amitriptyline, clomipramine, dothiepin, imipramine, mianserin, nomifensine, tranylcypromine, tryptophan, zimeldine	52% (HAMD decrease of ≥ 50%)	5/14
37	Gerken, 1985	N=7 (100% female) Inclusionary criteria: primary endogenous MDD according to the DSM-III	Cortisol after DST (blood)	Amitriptyline, lofepramine	71% (HAMD score ≤ 6)	7/14

		Exclusionary criteria: medical illness, cerebral atrophy, alcohol withdrawal, pregnancy, significant weight loss, steroid-containing drugs, anticonvulsive drugs, barbiturates				
38	Arato, 1984	N=74 (100% female) Inclusionary criteria: MDD according to RDC, HAMD score ≥ 18 Exclusionary criteria: medical illnesses influencing the DST, drugs	Cortisol after DST (blood)	Amitriptyline, dipenzepine, imipramine, maprotiline	64% (HAMD decrease of ≥ 50%)	3/14
39	Frank, 1984	N=34 (82% female) Inclusionary criteria: primary recurrent unipolar depression according to RDC, HAMD score ≥ 15 and Raskin	Basal cortisol (serum)	Combined treatment	68% (HAMD score ≤ 10)	7/14

	Depression Scale score ≥ 7 Exclusionary criteria: significant cardiovascular, renal, liver, or endocrine disease, epilepsy, glaucoma, organic brain syndrome, lifetime Briquet's disorder, panic disorder, generalised anxiety disorder, obsessive-compulsive disorder, phobic disorder, or antisocial personality disorder, mental retardation, psychotropics within 14 days, medical history precluding the use of tricyclic antidepressants	

ACTH = adrenocorticotropic hormone, AVP = arginine vasopressin, BDI = Beck Depression Inventory, CAR = cortisol awakening response, CBG = corticosteroid-binding globulin, CGI = Clinical Global Improvement, CRH = corticotropin releasing hormone, CSF = cerebrospinal fluid, DEX/CRH = dexamethasone/corticotropin releasing hormone, DST = dexamethasone suppression test, ECT = electroconvulsive therapy, GR = glucocorticoid receptor, HAMD = Hamilton Rating Scale for Depression, HPA = hypothalamic-pituitary-adrenal, IDS-C = Inventory of Depressive Symptoms – Clinician-Rated,

MADRS = Montgomery-Asberg Depression Rating Scale, MAO = monoamine-oxidase, MDE = major depressive episode, MDD = major depressive disorder, MINI = Mini International Neuropsychiatric Interview, RDC = Research Diagnostic Criteria, SCID = Structured Clinical Interview for the Diagnostic and Statistical Manual