



HPA dysfunction

Introduction

The biological response to stress is mediated through the Hypothalamic-Pituitary-Adrenal (HPA) axis and the sympathetic nervous system. Cortisol and the steroid hormone dehydroepiandrosterone (DHEA) and its sulfate form DHEA-S are important for elucidating the role of HPA dysfunctions in PTSD. Stress is a threat to the body's ability to regulate internal processes following exposure to an adverse event. People adapt physiologically and behaviourally in response to stress to re-establish internal balance. Altered HPA axis activity can be detrimental to physical and psychological health.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with PTSD. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. When multiple copies of review topics were found, only the most recent and comprehensive version was included. We prioritised reviews with pooled data for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis¹. Reviews with less than 50% of items checked have been excluded from the library. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation ([GRADE](#)) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low

if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)². The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found two systematic reviews that met our inclusion criteria^{3, 4}.

- Moderate to high quality evidence found small decreases in morning and 24hour cortisol levels in people with PTSD compared to controls. The effect was larger in studies with non-trauma exposed controls than in studies with trauma exposed controls.
- Moderate quality evidence found no significant changes in cortisol levels or in the cortisol awakening response following psychosocial treatments for PTSD.
- Moderate to high quality evidence found no significant differences in DHEA or DHEA-S levels compared to controls, apart from higher evening DHEA levels in people with PTSD when compared to non-trauma exposed controls.



HPA dysfunction

Schumacher S, Niemeyer H, Engel S, Cwik JC, Knaevelsrud C

Psychotherapeutic treatment and HPA axis regulation in posttraumatic stress disorder: A systematic review and meta-analysis

Psychoneuroendocrinology 2018; 98: 186-201

[View review abstract online](#)

Comparison	Effects of treatment on HPA dysfunction in people with PTSD.
Summary of evidence	Moderate quality evidence (unclear sample size, some inconsistency, precise, direct) found no significant differences in cortisol levels or the cortisol awakening response following psychosocial treatments.
Cortisol	
<i>There were no significant differences in cortisol levels from pre-treatment to post-treatment; 3 studies, N not reported, $g = -0.07$, 95%CI -0.36 to 0.21, $p = 0.621$, $I^2 = 45%$, $p = 0.142$ Results were similar for the cortisol awakening response.</i>	
Consistency in results[‡]	Moderate inconsistency
Precision in results[§]	Precise
Directness of results	Direct

Schumacher S, Niemeyer H, Engel S, Cwik JC, Laufer S, Klusmann H, Knaevelsrud C

HPA axis regulation in posttraumatic stress disorder: A meta-analysis focusing on potential moderators

Neuroscience and Biobehavioral Reviews 2019; 100: 35-57

[View review abstract online](#)

Comparison	Blood, urine, or salivary cortisol and DHEA levels in people with PTSD vs. controls.
Summary of evidence	Moderate to high quality evidence (large samples, inconsistent, mostly precise, direct) found small decreases in morning and 24hour cortisol levels in people with PTSD compared to controls. The effect was larger in studies with non-trauma exposed controls than in studies with trauma exposed controls.



HPA dysfunction

	<p>There were large decreases in cortisol levels after dexamethasone administration in people with PTSD. There were no significant differences in DHEA or DHEA-S levels compared to controls, apart from higher evening DHEA levels in people with PTSD when compared to non-trauma exposed controls.</p>
Cortisol	
<p><i>Small effects showed morning and 24hour cortisol levels were reduced in people with PTSD compared to controls;</i></p> <p>Morning: 43 studies, N = 2,003, $g = -0.21$, 95%CI -0.42 to -0.01, $p = 0.038$, $I^2 = 79\%$ 24hour: 22 studies, N = 749, $g = -0.31$, 95%CI -0.60 to -0.03, $p = 0.033$, $I^2 = 71\%$</p> <p>The effect sizes were larger in studies with non-trauma exposed controls than in studies with trauma exposed controls.</p> <p>There were no differences in evening cortisol levels, and no consistent effects of moderators (measures, samples, medication status, study quality).</p> <p>There were large decreases in cortisol levels after dexamethasone administration.</p>	
DHEA	
<p><i>There were no significant differences in morning DHEA levels;</i></p> <p>7 studies, N = 474, $g = 0.25$, 95%CI -0.15 to 0.65, $p = 0.212$, $I^2 = 78\%$</p> <p>The effect sizes were larger in studies with non-trauma exposed controls than in studies with trauma exposed controls.</p> <p>There were no differences in evening DHEA levels, apart from the comparison with non-trauma exposed controls where people with PTSD had higher evening DHEA levels.</p>	
DHEA-S	
<p><i>There were no significant differences in morning DHEA-S levels;</i></p> <p>5 studies, N = 353, $g = 0.30$, 95%CI -0.26 to 0.86, $p = 0.290$, $I^2 = 85\%$</p>	
Consistency in results	Inconsistent
Precision in results	Precise, apart from DHEA-S
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, g = Hedges' standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, p = statistical probability of obtaining that result, vs. = versus



HPA dysfunction

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small⁵.

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified

(100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect⁵.

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if $RR > 2$ or < 0.5 and a large effect if $RR > 5$ or < 0.2 ⁶. InOR stands for logarithmic OR where a InOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship



HPA dysfunction

between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforeseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (b) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula⁵;

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence

limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed⁷.

|| Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.



HPA dysfunction

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADE Working Group (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Schumacher S, Niemeyer H, Engel S, Cwik JC, Knaevelsrud C (2018): Psychotherapeutic treatment and HPA axis regulation in posttraumatic stress disorder: A systematic review and meta-analysis. *Psychoneuroendocrinology* 98: 186-201.
4. Schumacher S, Niemeyer H, Engel S, Cwik JC, Laufer S, Klusmann H, *et al.* (2019): HPA axis regulation in posttraumatic stress disorder: A meta-analysis focusing on potential moderators. *Neuroscience and Biobehavioral Reviews* 100: 35-57.
5. Cochrane Collaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
6. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
7. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 3.2 for Windows*