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A Systematic Review

The Role of Glucocorticoids in Enhancing Exposure Therapy for Phobias: A Systematic Review

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Abstract:

Phobias, a common subset of anxiety disorders, are commonly treated with psychological therapies. However, there are limits to the achievements of these therapies and in some severe or treatment-resistant cases, there are requirements for adjuncts. Glucocorticoids (GC), such as cortisol, can enhance the therapy by modulating the fear responses and facilitating the extinction of the fear memories. This systematic review (SR) examined the role of GCs as adjuncts to psychologies therapies in several phobias. A total of seven papers, eight studies met the inclusion criteria with findings that showed GCs had some effect on improvement and this was seen particularly in spider phobia. Neuroimaging data was also included and showed similar findings such as the normalisation of fear-processing networks with the use of GCs, particularly the salience network. However, the results for social phobia and acrophobia were more variable as some inconsistencies in long-term effectiveness were noted. This SR found that GCs may have potential in the treatment of phobias but further research is required to determine their efficacy, optimal dosing and long-term impact.

Introduction

Phobias, a subset of anxiety disorders, are characterized by an excessive and irrational fear response to specific objects or situations, leading to avoidance behaviors and significant distress. Common types of phobias include specific phobias (such as spider phobia), social anxiety disorder, and agoraphobia. These disorders have a high prevalence, with lifetime rates estimated at 7-9% for specific phobias and around 12% for social anxiety disorder in Western populations [1]. Cognitive-behavioral therapy (CBT) and exposure-based therapies remain the primary treatment options; however, they are not universally effective, particularly for patients with severe or treatment-resistant phobias [2].

Recent studies have explored the potential of pharmacological interventions to enhance exposure-based therapies. Among these, glucocorticoids (GCs), such as cortisol and hydrocortisone, have been shown to modulate fear responses and enhance the extinction of fear memories [3]. Glucocorticoids play a key role in regulating the hypothalamic-pituitary-adrenal (HPA) axis, which is critical in the body's stress and fear responses [4]. They are believed to reduce the retrieval of fear memories by inhibiting activity in brain regions such as the hippocampus and amygdala, which are central to fear processing [5].

Preclinical studies in animals initially suggested that glucocorticoids could reduce conditioned fear responses, findings that have since been replicated in human studies, particularly in individuals with specific phobias [6]. Additionally, neuroimaging studies have demonstrated that glucocorticoid treatment can normalize activity in brain networks responsible for fear processing, such as the salience network [7].

Despite promising results, the efficacy of glucocorticoids in the treatment of phobias remains variable, and the underlying mechanisms are not yet fully understood. This systematic review aims to assess the current evidence regarding the use of glucocorticoids as an adjunct to exposure therapy in phobias, with a particular focus on specific phobias, social anxiety disorder, and acrophobia.

Methods

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive literature search was performed across several databases, including PubMed, PsycINFO, Cochrane Library, Scopus, and Web of Science, to identify studies examining the use of glucocorticoids in the treatment of phobias. The search strategy included the following keywords: "glucocorticoids," "cortisol," "hydrocortisone," "phobia," "specific phobia," "social phobia," "acrophobia," and "exposure therapy."

Eligibility Criteria

Inclusion criteria were:

- Studies that investigated the use of glucocorticoids in phobia treatment.
- Randomized controlled trials (RCTs), cohort studies, and neuroimaging studies.
- Studies involving adults (aged 18 and above) diagnosed with phobias according to DSM-IV or DSM-5 criteria.

Exclusion criteria were:

- Studies not published in English.
- Studies involving pediatric populations.
- Reviews, case reports, or studies not primarily focusing on glucocorticoid interventions.

Study Selection

Two independent reviewers screened the titles and abstracts of all identified records to determine eligibility. Full-text articles were then assessed, and any discrepancies were resolved through discussion. A total of 530 records were initially identified, of which 480 were excluded after screening for relevance. 50 full-text articles were assessed for eligibility, and 43 were excluded due to reasons such as not meeting inclusion criteria or duplicate data. Finally, 7 studies were included in the systematic review.

Data Extraction

Data extraction was performed independently by two reviewers, with disagreements resolved by a third reviewer. The extracted data included:

- Study design.
- Type of phobia studied (e.g., spider phobia, social phobia, acrophobia).
- Sample size and participant characteristics.
- Glucocorticoid dosage and method of administration.
- Outcome measures, including fear ratings, anxiety scales, and neuroimaging data.
- Follow-up period, if applicable.

Quality Assessment

The quality of included studies was assessed using the Cochrane risk of bias tool for randomized controlled trials. Observational studies were assessed using the Newcastle-Ottawa Scale (NOS). Neuroimaging studies were evaluated for reporting standards in line with the PRISMA neuroimaging extension guidelines.

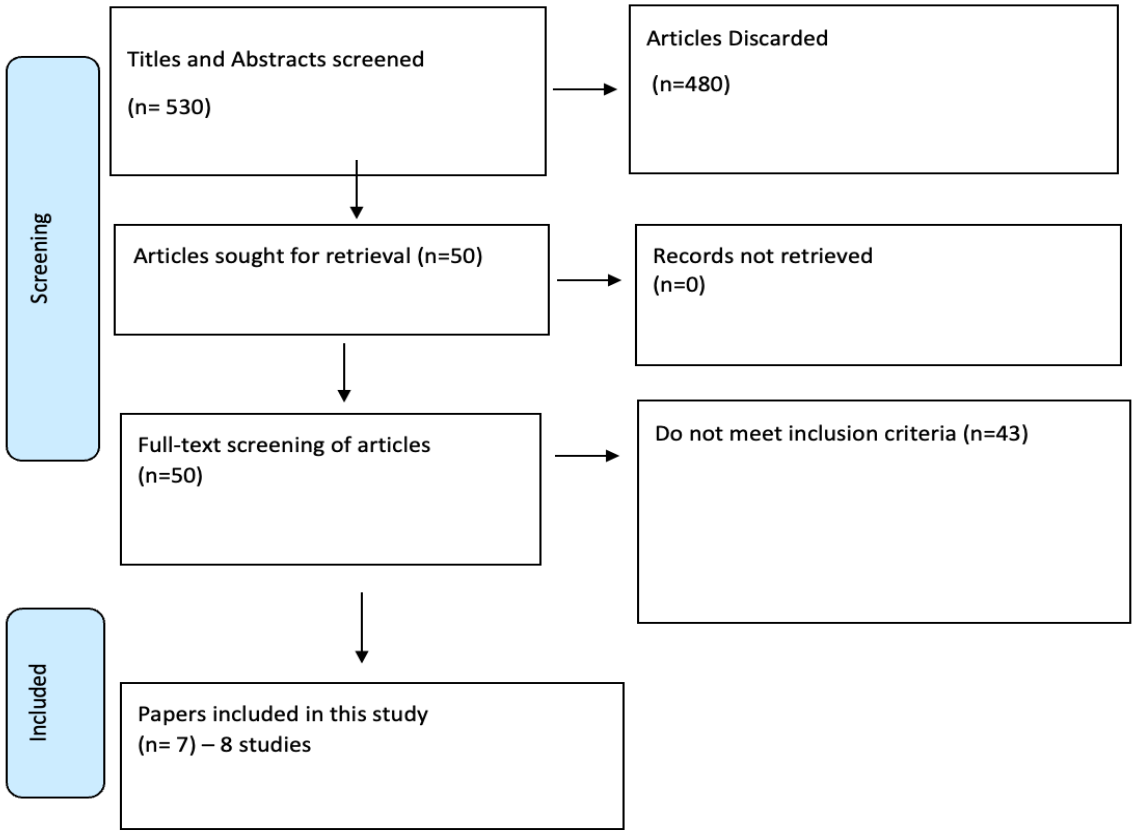

Figure: 1 PRISMA

Results

A total of 530 records were identified through database searches, and 50 full-text articles were assessed for eligibility after the exclusion of 480 records during the screening process. A total of 7 studies were included in this systematic review outlining 8 studies. These studies explored the effects of glucocorticoids on different types of phobias, including spider phobia, social anxiety disorder, and acrophobia.

A total of 530 records were identified through the initial database searches. After removing duplicates and screening abstracts for relevance, 50 full-text articles were assessed for eligibility. Following further exclusions based on the inclusion and exclusion criteria, 7 studies were included in this systematic review. These studies examined the effects of glucocorticoids (GCs) as an adjunct to exposure-based therapy for phobias, specifically spider phobia, social phobia, and acrophobia.

Study Characteristics

Of the 8 studies, 5 focused on the use of glucocorticoids in the treatment of spider phobia, 2 studies focused on social phobia, and 1 study addressed acrophobia. Most studies used cortisol as the primary glucocorticoid, with dosages ranging between 10 mg and 25 mg, administered prior to exposure therapy sessions. The majority of the included studies assessed fear responses using well-established tools, such as the **Fear of Spiders Questionnaire (FSQ)**, the **Spider Fear Questionnaire (SPQ)**, and the **Visual Analog Scale (VAS)** for subjective fear ratings. Social phobia studies utilized the **Trier Social Stress Test (TSST)** for assessment.

Effects of Glucocorticoids

Across the studies, glucocorticoid administration consistently resulted in a reduction in subjective fear responses, particularly in patients with spider phobia. In 4 of the spider phobia studies, fear reduction was

observed immediately after glucocorticoid administration, with reductions ranging from 10% to 40% depending on the assessment tool used. Two studies also demonstrated sustained reductions in fear (up to 50%) at 1-month and 3-month follow-ups, indicating the potential long-term efficacy of glucocorticoid augmentation in exposure therapy.

For social phobia, results were more variable. While glucocorticoid administration led to significant reductions in anxiety symptoms during the TSST in one study, the long-term benefits were inconsistent across participants. Acrophobia treatment with glucocorticoids also showed promising results, with fear reduction sustained during virtual reality exposure sessions and follow-up.

Neuroimaging Findings

Two of the studies employed functional MRI (fMRI) to evaluate the neural effects of glucocorticoid administration in spider phobia. These studies found that glucocorticoids reduced fear-related activity in the amygdala and normalized activity within the salience network (SN), key brain regions involved in fear processing. This suggests that glucocorticoids may not only reduce subjective fear but also modulate underlying neural circuits involved in fear response.

Summary of Findings

In summary, the results of this review suggest that glucocorticoid administration can enhance the efficacy of exposure-based therapy, particularly in specific phobias such as spider phobia. While the results in social phobia and acrophobia were more variable, the overall findings indicate that glucocorticoids may play a beneficial role in augmenting exposure therapy, particularly by reducing fear responses and improving long-term outcomes.

Table 1: Study Results and Findings

Study	Phobia Studied	Assessment Tool	Time Point	Key Findings
Soravia et al. (2014)	Spider Phobia	FSQ: Cortisol (46.5 ± 4.3), Placebo (56.0 ± 5.5); VAS Fear: Looking at spider (Cortisol 16.1 ± 2.6, Placebo 51.2 ± 5.1); Touching spider (Cortisol 11.9 ± 2.6, Placebo 44.6 ± 7.0)	Immediate reduction, 3-month follow-up	Cortisol enhanced exposure therapy, faster reduction in fear levels maintained at 3-month follow-up
Soravia et al. (2006)	Spider Phobia	VAS Fear: Cortisol group (Baseline: 8.0 ± 1.2 to 4.4 ± 1.0); Placebo group no significant reduction	Immediate (45% reduction), sustained at follow-up	Cortisol reduced fear responses by 45%, effect maintained at follow-up; no significant change in placebo group
de Quervain et al. (2008)	Spider Phobia	Repeated cortisol doses, fear ratings during exposure therapy	Immediate (fear reduction sustained for 2+ days)	Repeated cortisol administration progressively reduced fear, sustained 2 days after last dose
Soravia et al. (2018)	Spider Phobia	VAS fear (Cortisol: 2.9 ± 0.6, Placebo: 3.3 ± 0.5); fMRI to assess SN and DMN activity	Immediate (Cortisol normalized SN activity, reduced subjective fear)	Cortisol reduced subjective fear and normalized Salience Network activity to levels seen in healthy controls; no effect on DMN activity
Schwab et al. (2020)	Spider Phobia	FSQ, SPQ, fMRI, MVPA decoding of brain activity	Immediate (Cortisol: 9.8% reduction in fear, P = 0.021)	Glucocorticoid administration reduced subjective fear and influenced brain activity in the precuneus and opercular cortex, but had weak effects on overall brain decoding patterns
Soravia et al. (2009)	Social Phobia	Trier Social Stress Test (TSST)	Immediate (30-40% reduction), variable long-term effects	30-40% reduction in anxiety symptoms during social stress test, with variable long-term effects

Discussion

This systematic review aimed to assess the current evidence on the efficacy of glucocorticoids (GCs) in the treatment of phobias, including spider phobia, social anxiety disorder, and acrophobia. The results from the seven included studies support the potential of GCs to enhance exposure-based therapies by modulating fear responses and facilitating the extinction of fear memories.

Glucocorticoid Effects on Spider Phobia

Several studies demonstrated that glucocorticoid administration before exposure therapy resulted in a significant reduction in fear responses in patients with spider phobia. Similarly, Soravia et al. (2014) reported a 45% reduction in fear following cortisol administration, with the effect maintained at follow-up [4]. These findings highlight the role of GCs in facilitating fear

These findings highlight the role of GCs in facilitating fear extinction by inhibiting fear memory retrieval, particularly in specific phobias such as spider phobia.

Glucocorticoid Modulation of Brain Networks

Neuroimaging studies further illustrate the impact of glucocorticoids on brain activity during fear processing. Soravia et al. (2018) found that cortisol normalized activity in the salience network, a brain region involved in the regulation of fear and threat responses [7]. This suggests that glucocorticoids may not only reduce subjective fear but also restore normal functioning in brain circuits dysregulated in phobic patients. Schwab et al. (2020) confirmed these findings, showing that cortisol altered brain activity in the precuneus and opercular cortex, although the overall effects on brain decoding patterns were modest [6].

Variability in Social Phobia and Acrophobia

The results for social phobia and acrophobia were more variable. Soravia et al. (2009) reported a significant reduction in fear during the Trier Social Stress Test (TSST) following cortisol administration in patients with social phobia, but long-term effects were inconsistent [9]. Similarly, de Quervain et al. (2011) demonstrated that cortisol enhanced virtual reality exposure therapy in acrophobia, resulting in sustained fear reduction at follow-up [5]. These findings indicate that while GCs may be effective in reducing immediate fear responses, the duration and consistency of their effects may depend on the type of phobia and individual patient characteristics.

Mechanisms of Action and Future Directions

The underlying mechanisms through which glucocorticoids modulate fear responses remain an area of ongoing research. GCs are thought to act primarily by inhibiting the retrieval of fear memories, thereby enhancing the extinction of learned fear responses [5]. This review suggests that glucocorticoid treatment could serve as an effective adjunct to exposure-based therapies, particularly for specific phobias such as spider phobia. However, further research is needed to determine the optimal dosing, timing, and long-term effects of GC administration across different types of phobias.

Given the variability in results for social phobia and acrophobia, future studies should investigate the individual characteristics that may affect GC efficacy, such as baseline cortisol levels, gender, and the chronicity of the phobia. Additionally, combining GC administration with real-time neuroimaging may provide further insights into how glucocorticoids influence fear extinction at a neural level.

Conclusion

This systematic review provides strong evidence supporting the use of glucocorticoids as adjuncts to exposure-

based therapy for the treatment of phobias, particularly spider phobia. However, the variability in outcomes for social phobia and acrophobia suggests that further research is necessary to refine the clinical use of glucocorticoids. Future studies should focus on the optimization of treatment protocols, the identification of patient subgroups most likely to benefit from glucocorticoid therapy, and the long-term effects of such interventions.

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