INPLASY

A systematic review and meta-analysis of cortisol responses in psychosis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 August 2024 and was last updated on 29 August 2024.

INTRODUCTION

Review question / Objective To observe for variation in cortisol responsivity to psychological and physiological stressors in patients with psychosis compared to healthy controls.
P: Patients with psychosis
I: Physiological and Psychological stressors in an experimental setting
C: Healthy controls with no diagnosed psychiatric disorder
O: Cortisol levels post-stressor and overall cortisol differences in response to experimental stressor intervention.

Rationale The HPA axis is an integral physiological system involved in governing the body's response to stress. HPA-axis dysregulation and hypercortisolemia have been previously observed in patients with psychosis, which is supported by an extensive body of literature. The complex interaction between stress and psychosis has yet to be fully elucidated, but the role of stress in precipitating the onset and relapse of psychosis has been now widely recognised by the growing body of literature focusing on the impact of psychosis on Hypothalamic-Pituitary Adrenal (HPA) axis activity. This meta-analysis aims to study the changes in cortisol in response to stressful stimuli in patients with psychosis, relative to healthy controls. We aim to explore the presence of any discernible variation in cortisol reactivity in response to physiological and psychological stressors. We aim to investigate potential correlations with cortisol levels and other demographic and clinical factors such as: age, sex, medication, severity of psychotic symptoms and duration of diagnosis. No prior studies have demonstrated differential cortisol reactivity in response to physiological versus psychological stressors. Distinguishing any potential differential cortisol reactivity to stress in psychosis may allow for further understanding of the neuropsychopathology of psychosis, and may lend

itself to further therapeutic advancements to target these stress responses.

Condition being studied Psychosis is a complex psychiatric syndrome, which results in impairment of reality perception, involving hallucinations, delusions and inappropriate or abnormal behaviours among other symptoms (1). The median lifetime prevalence of psychosis has been reported to be 7.49 per 1,000 individuals (2). These symptoms may arise as part of a primary psychotic syndrome, such as Schizophrenia (SCZ), and schizoaffective disorder (SAD), or may arise in the context of a pre-existing psychiatric or mood disorder, such as manic or depressive disorders (3). The complex interaction between stress and psychosis has yet to be fully elucidated, but the role of stress in precipitating the onset and relapse of psychosis has been now widely recognised by the growing body of literature focusing on the impact of psychosis on Hypothalamic-Pituitary Adrenal (HPA) axis activity (4).

METHODS

Search strategy Initially, a systematic literature search will be conducted on Google Scholar and PubMed. This search will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature search will include papers published between 1949 and 2021. The following keywords will be searched in the database to retrieve relevant articles containing the following search profile: “cortisol OR HPA OR hypothalamic pituitary adrenal OR awakening response” AND “psychosis OR mania OR schizophrenia OR psychotic depression OR schizoaffective” AND “stress OR dexamethasone suppression test OR trier social stress test” OR “physiological stress” OR “psychological stress”.

Participant or population Patients with a diagnosis of psychosis according to International Classification of Diseases (ICD) or Diagnostic and Statistical Manual (DSM) criteria.

Intervention Interventions will include a variety of psychological and physiological stressful stimuli. Cortisol levels will be measured via serum cortisol or salivary cortisol post-stressor ± pre-stressor.

Comparator Healthy controls with no previously diagnosed psychiatric disorder, who were not defined as being high-risk for psychosis, and had no previously diagnosed neurological or endocrine disorder.

Study designs to be included Case-Control trialsRandomised Control Trials.

Eligibility criteria Inclusion criteria are as follows:: English speaking, human studies, patients with a diagnosis of psychosis according to International Classification of Diseases (ICD) or Diagnostic and Statistical Manual (DSM) criteria, involved exposure of both psychosis and control participants to a stressor stimulus and measured cortisol levels before and/or after stressor exposure. Additionally, we will exclude all studies that lacked healthy controls, studies involving endocrine disorders, studies involving genetic disorders, and studies performed on animals.

Information sources Initially, a systematic literature search will be conducted on Google Scholar and PubMed. This search will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Main outcome(s) Cortisol levels after stressor exposure will be the primary outcome of interest. Where available, cortisol levels prior to stressor exposure will also be collected to allow for calculation of overall cortisol difference in response to the stressful stimulus. Mean and standard deviations (SD) for cortisol levels will be collected for both psychosis and control groups. Cohen’s D effect sizes and F-values for cortisol reactivity to stressors, where available will also be collected.
Cohen’s D effect size for post-stressor cortisol levels as well as overall cortisol difference of patients with psychosis versus controls will be calculated. This will allow for standardisation and comparison effect size between included studies.

Additional outcome(s) Information on population demographics (age, sex), psychosis severity (as measured through conventional clinical/research assessment scales such as the Brief Psychiatric Assessment Scale (BPRS), Positive and Negative Syndrome Scale (PANSS)), medication details (proportion medicated, medication type) will be collected.

Data management Available papers will be screened by two independent screeners. Data will be extracted from available papers and collected into each screener’s individual spreadsheet. This will be compared and conflicts will be settled by a third, more senior reviewer. The data will then be uploaded to a shared spreadsheet for universal access by all screeners.

Quality assessment / Risk of bias analysis The quality of the studies eligible for inclusion will be

evaluated using the modified Newcastle-Ottawa Scale (mNOS) (24). Studies with NOS scores 0–3, 4–6 and 7–9 will be considered as low, moderate and high quality, respectively. Furthermore, Funnel and Galbraith plots will be formulated to quantitatively assess for publication bias.

Strategy of data synthesis All statistical analyses will be conducted using SPSS v28.0 (22). We predict systematic differences in methodology and study characteristics, and so a Restricted Maximum Likelihood (REML) random effects model will be used for subgroup meta-analyses. Using a 95% Confidence Interval (CI) and a significant p-value of 0.05, confidence intervals and cumulative levels of significance will also be calculated for each subgroup pooled result.
Cumulative effect sizes for each stressor category, as well as each specific intervention type will be calculated. Meta-regressions will be performed using the demographic characteristics (age, sex, diagnosis length, proportion medicated, severity of psychosis as determined by clinical assessment scales). These characteristics will be regressed against effect sizes for post-stressor and pre/post stressor differences.
Statistical heterogeneity will be calculated by I2 values for each subgroup. Low, moderate and high heterogeneity will be indicated by an I2 score of 25, 50, 75% respectively.

Subgroup analysis To combat the anticipated statistical heterogeneity due to the systematic differences in patient characteristics and study methodology, various subgroup analyses were performed. All patients with psychosis were divided into one of four diagnostic categories – Schizophrenia, First Episode Psychosis, or other forms of psychosis (including major depressive disorder with psychosis, senile psychosis or studies included multiple psychotic disorders as a single grouping). Furthermore, another subgroup analysis was performed based on the method of cortisol collection (blood and salivary cortisol).

Sensitivity analysis Modified Newcastle-Ottawa Scores will be calculated for each included study to assess quality of eligible studies. Furthermore, Funnel and Galbraith plots will be formulated to quantitatively assess for publication bias. We predict systematic differences in methodology and study characteristics, and so a Restricted Maximum Likelihood (REML) random effects model will be the most suitable for this analysis.
To counter anticipated heterogeneity and ensure robustness of the data generated, further subgroup analyses will be conducted using a REML random effects model. This will allow for splitting of data into subgroups based on stressor subtype, diagnosis subgroup (based on ICD11/DSM V defined psychosis subtype) and method of collection (Salivary/Serum cortisol) to explore the consistency of our findings.
We will conduct supplementary analyses excluding any studies that appear to be statistical outliers to see how this affects the overall findings.

Language restriction Only English language publications, or publications with an accessible English translation will be included.

Country(ies) involved Ireland.

Keywords HPA-axis; Psychosis; Cortisol; Stress; Schizophrenia; Schizoaffective disorder.

Dissemination plans This study will be published in a peer-reviewed, open access journal. We plan to present the findings of this study at relevant psychiatry and neuroendocrinology conferences.

Contributions of each author
Author 1 - Linda Kelly - Involved in preliminary data collection, statistical analysis and drafting of initial manuscript.
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