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Psychological and pharmacological treatments of intermittent explosive disorder: a meta-analysis protocol

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ABSTRACT

Introduction Intermittent explosive disorder (IED) is characterised by recurrent, sudden episodes of impulsive aggression that are disproportionate to the provocation. The condition's management remains challenging due to the variability in treatment efficacy and the absence of Food and Drug Administration-approved interventions specifically for IED. This meta-analysis aims to evaluate the effectiveness of existing treatments for IED.

Methods and analysis Adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a comprehensive literature search was conducted in November 2023, yielding 17 randomised controlled trials after screening and eligibility assessments. Studies were included based on participants' confirmed diagnosis of IED, sufficient statistical power and provision of data for effect size calculation. Interventions analysed included pharmacological treatments, psychotherapies and combination therapies, with an emphasis on cognitive–behavioural therapy and selective serotonin reuptake inhibitors. Quality assessment was performed using the Cochrane Risk of Bias Tool.

Ethics and dissemination Given that our study is a synthesis of published data, ethical approval from a research ethics committee is not required. Nevertheless, the methodology of this review was designed to ensure full transparency and accountability. All efforts have been made to respect the confidentiality and intellectual property rights of the original data sources. Any ethical issues encountered during the data collection process were addressed in accordance with the guidelines of the Declaration of Helsinki. As this research involves the analysis of existing published data, there are no direct safety concerns related to patient interactions. Our primary focus has been on ensuring the secure handling and processing of data to uphold the ethical standards set by previous original studies. To ensure the findings of our meta-analysis reach both the academic community and the public effectively, we aim to submit our findings to peer-reviewed journals within the fields of psychology to ensure rigorous review and broad academic dissemination.

PROSPEO registration number CRD42024497587.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Inclusion of randomised controlled trials (RCTs): By focusing exclusively on RCTs, the strongest level of evidence for therapeutic interventions is considered, which strengthens the validity of the results and conclusions drawn.
⇒ Consideration of comorbidities: Including studies where participants have comorbid conditions like depression reflects the real-world complexity of intermittent explosive disorder, making the findings more applicable to typical clinical populations.
⇒ Potential for publication bias: Despite efforts to mitigate this, the possibility of publication bias, as suggested by the funnel plot analysis, may still skew the results.
⇒ Heterogeneity of studies: Variability in terms of interventions, outcome measures and participant characteristics across studies can make it challenging to draw definitive conclusions about the effectiveness of treatments.

INTRODUCTION

Intermittent explosive disorder (IED) is characterised by sudden and disproportionate outbursts of anger in response to minor daily provocations.[1] These outbursts can manifest as verbal aggression (eg, temper tantrums, tirades and arguments) or physical aggression towards the property, animals or other individuals.[2] These angry outbursts are often spontaneous and not premeditated. After the outburst, the individual may feel remorse, regret or embarrassment about their actions.[1]

The global prevalence of IED is estimated to be between 4% and 6%, depending on the diagnostic criteria used.[1 3] Notably, there has been a rise in IED diagnoses over the past decade,[3 4] possibly attributed to changes in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) diagnostic criteria,[2 5] which now include verbal aggression as an important diagnostic criterion for IED.[2 3] This diagnostic criteria adjustment may have led to an increased number of individuals meeting the criteria for IED.[6] Furthermore, the overlap between IED and other mental health disorders has historically been a challenge in diagnosis. However, as understanding of comorbidities grows and clinicians become more adept at identifying multiple disorders,

there has been an increase in diagnosing IED, especially in cases where it coexists with other disorders.[7]

Among the psychiatric disorders that exhibit the highest comorbidity with IED are mood disorders (such as major depressive disorder and bipolar disorder), anxiety disorders (including generalised anxiety disorder and panic disorder) and substance use disorders.[8] The presence of these comorbid conditions complicates the clinical picture and influences treatment outcomes. For instance, individuals with both IED and a mood disorder may exhibit more severe symptoms and have a poorer prognosis compared with those with IED alone.[9]

Behavioural issues associated with IED may improve with age,[3] For instance, aggressive behaviours, both physical and verbal, tend to decrease as individuals mature. This improvement can be attributed to several key factors. First, developmental changes in emotional regulation play a crucial role. As individuals age, their brains become more adept at managing emotions and controlling impulses, leading to fewer aggressive outbursts and better handling of agitation.[10] Second, socialisation processes significantly contribute to this decline. Increased social interactions and experiences help individuals understand and adhere to social norms, thereby reducing aggressive behaviours.[11]

However, adolescents with IED are still at a higher risk of social difficulties, academic underperformance and criminal behaviour.[12 13] Although aggressive behaviour is widespread and the DSM-5-TR recognised IED as a disorder primarily characterised by impulsive aggression,[5] there are currently no interventions approved by the US Food and Drug Administration specifically for reducing these behaviours.[4] Current treatment options for IED are diverse, yet their efficacy varies and is not universally established due to the complexity of the disorder.[14–16]

Psychotherapy, especially cognitive–behavioural therapy (CBT), is often the primary treatment for IED.[14 17 18] CBT is a structured, goal-oriented therapy that involves working with a therapist to understand how thoughts affect actions, aiming to change negative thought patterns and behaviours to healthier ones.[18] Specific techniques used in CBT for IED include cognitive restructuring, relaxation training, coping skills training and relapse prevention.[14 17 18] These techniques are designed to help individuals with IED manage negative situations in daily life and prevent aggressive impulses that can trigger explosive outbursts.

Regarding pharmacological treatments, certain medications can increase the threshold at which situations trigger angry outbursts in people with IED.[19] Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is the most studied medication for treating IED.[3 4 6 13 19] Other medications that have shown promise in treating IED include phenytoin, lithium, oxcarbazepine and carbamazepine.[20]

Despite these options, a critical gap remains in the systematic evaluation and comparison of these treatments. Conducting a meta-analysis in this field is, therefore, essential as it would provide a more comprehensive understanding of the effectiveness of current treatments by aggregating data from multiple studies. This aggregated analysis could identify the most effective interventions, inform better practices and guide future research directions for IED. This study aimed to perform a comprehensive meta-analysis to evaluate the effectiveness of various treatments for IED. It specifically aimed to compare these treatments' efficacy against waitlist and placebo controls, examine differences in attrition rates, assess the durability of treatment gains at follow-up and identify emerging promising treatments for IED.

METHOD

Search strategy

Following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we searched the following databases: CENTRAL, Embase, Medline, PsycINFO, PsycEXTRA and Global Health in November 2023. The reference list of included studies was also manually searched. In sum, the search turned out 1450 studies imported for screening. After removing duplicates, 1442 studies were screened, and 34 studies were assessed for eligibility by conducting full-text screening. 11 studies were included in this meta-analysis from databases searching. A manual search for references turned out six additional included studies. A total of 17 randomised controlled trial (RCT) studies are included in this meta-analysis. The article selection process involved independent evaluations by two reviewers (FL and XY), resulting in an inter-rater reliability score of 0.83 for title and abstract screenings. For full-text screenings, the inter-rater reliability was determined to be 0.78. In instances of discrepancies, resolution will be undertaken by a third reviewer (Yi Xuan Li), who will make the final inclusion decision. This meta-analysis is registered with the International Prospective Register of Systematic Reviews (PROSPEO) under the registration number: CRD42024497587. The exact

Table 1 Comprehensive search terms for RCT research

Category	Search terms
IED	Intermittent Explosive Disorder OR IED OR Impulsive*
Treatment	Treatment OR Intervention OR Therapy OR Interve*
Pharmacological	Drug OR Pharma* OR Psychopharm* OR Antidepressants OR Mood stabilizers
Psychological	CBT OR Cognitive Behavioral Therapy OR Anger management* OR behavio*
Others	Randomized controlled trial OR Randomised controlled trial OR RCT OR Integrated treatment

IED, intermittent explosive disorder; RCT, randomised controlled trial.

search terms included are listed in table 1 and an exemplary search result is provided in online supplemental material I.

Inclusion and exclusion criteria

Studies were assessed based on the following inclusion criteria: First, all participants in the studies were required to have a confirmed diagnosis of IED, adhering to the diagnostic standards of either the DSM or International Classification of Diseases (ICD), established through structured or unstructured clinical interviews. Second, a minimum participant threshold was set, with each study needing to include at least four patients, ensuring a baseline level of statistical validity. Third, the studies are required to provide a detailed dataset that includes, at a minimum, pretrial and post-trial means, SDs, sample sizes (n's) of outcome measures and a clear description of the nature of these outcome measures as this information is essential to facilitate the accurate computation of effect sizes, trial durations and additional subgroup analyses. In instances where this level of detail was not reported, further information was requested directly from the study authors to ensure the completeness of the necessary statistics. Only randomised clinical trials focusing on intervention strategies for IED were considered. The scope of eligible interventions was broad yet specific: it encompassed oral medications (administered in either fixed or flexible dosages), various psychological or behavioural interventions (including lifestyle modifications like exercise) and combination therapies.

To provide a comprehensive overview and counteract publication bias, our study will include unpublished data alongside peer-reviewed articles. We will identify potential contributors by reviewing authors of relevant literature, a standardised email will be used to directly contact these authors to request unpublished data related to RCT studies on IED treatment. Unpublished data will be included if it meets established relevance, methodology and quality criteria comparable to those for published studies. This strategy will enhance the depth and breadth of our analysis, ensuring a robust dataset that encompasses the most current and comprehensive insights available.

The exclusion criteria include studies primarily targeting other disorders, such as substance abuse, to maintain a clear focus on IED. However, studies were included if participants while primarily diagnosed with IED, also met criteria for other comorbid disorders like depression. This inclusion acknowledges the complex, often overlapping nature of mental health disorders. Drugs no longer in the market, such as brofaromine, were excluded if only compared with a placebo in trials. This exclusion criterion was applied because these studies would not yield insights into currently available treatments, ensuring that the meta-analysis remained practical and relevant to current clinical practices. There are no other eligibility restrictions on gender/sex or age.

Data extraction

The following variables will be extracted and coded from the studies meeting inclusion criteria: author, publication year, comparisons (including the type of intervention (eg, CBT, medication) and the characteristics of the control condition (eg, wait-list, placebo, alternative treatment), time point of post-treatment measures, pharmacological or psychotherapeutic intervention, mean age and gender of the participants, diagnosis criteria (eg, DSM and ICD), treatment dosage (medication dosage or the number of therapy sessions) and treatment duration (eg, weeks of treatment), outcome variables and measurement tools (primary and secondary outcome variables including the specific measures used to assess these outcomes, time point of outcome assessment (the time point of post-treatment measures and any follow-up measurement intervals).

Risk of bias (quality) assessment

Two reviewers (FL and XY) will perform a quality appraisal of each study independently using the Cochrane Risk of Bias Tool. This tool is specifically designed to assess the risk of bias in the results of RCTs. It evaluates several domains such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. We also used the PRISMA-Protocol checklist for quality assurance, which is included in online supplemental material II.

Type of outcome measure

The primary outcome focus is on reducing aggressiveness in patients with IED, with any additional relief from relevant symptoms also being carefully assessed and interpreted. Validated outcome instruments of IED (eg, Overt Aggression Scale Modified, The State-Trait Anger Expression Inventory-2) will be considered. To be included, studies must report a quantitative measure of the effect of the intervention on IED. Additionally, the rates of full remission will be reported as the primary outcome, as it serves as an important indicator of the effectiveness of IED treatments.

Statistical analyses

Data will be entered and analysed by the Comprehensive Meta-analysis software, V.2.2.057. In order to calculate Cohen's d effect sizes that reflect the relative change from pretest to post-test in the intervention versus control condition. We will calculate standardised mean difference effect sizes that adjust for pretest mean differences, which expresses the size of the intervention effect in each study relative to the variability observed in that study and we will do it by dividing the difference in mean outcomes between groups by the SD of outcomes among participants.

Among the studies, heterogeneity will be assessed by Q and I^2 statistics. The Q test examines whether there is more heterogeneity in the results than could be explained

by chance alone, which would be indicated by a corresponding p value lower than 0.05. The I^2 describes the proportion of total variation caused by heterogeneity and is used as a descriptive supplement to Q. I^2 values <25% are interpreted as small, <50% as medium and >75% as a large heterogeneity.

The calculation of random effects will be conducted for the overall effect sizes. We calculated random effects only for the contrast analyses, which assumes that the studies are drawn from populations that differ from each other.

To assess publication bias within our meta-analysis, which included a small collection of studies ranging from 5 to 20, the Luis Fuyura-Kanamori (LFK) index will be employed.[17] This metric is particularly sensitive in detecting asymmetry of effect sizes in such small samples. A value near 0 on the LFK index indicates symmetry, suggesting a low likelihood of publication bias. Conversely, an LFK index beyond the thresholds of ±1 signals significant asymmetry, hinting at potential publication bias. Alongside the LFK index, Doi plots will be created to visually represent the asymmetry and further substantiate the findings. This approach was favoured over traditional methods such as funnel plots and fail-safe N procedures due to the LFK index's superior sensitivity in small sample scenarios, providing a more reliable indication of publication bias.

Our meta-analysis will encompass subgroup analyses to explore the variability and targeted effectiveness of treatments for IED. These analyses are structured to evaluate three main areas: first, the type of treatment, where we will differentiate between psychological treatments, pharmacological interventions and their combination, aiming to identify distinct effects each may have. Second, we will consider the duration of treatment to determine if the length of a treatment regimen influences the sustainability of its effects. Lastly, follow-up duration will be scrutinised to assess the enduring impact of treatments and capture the long-term trajectory of treatment benefits. This approach will provide a comprehensive understanding of how different treatment modalities perform across various timescales. The planned start date for the data extraction and data analysis is August 2024.

Patient and public involvement

None. This study is a meta-analysis based on previously published data, and as such, there was no direct involvement of patients or the public in the design or conduct of the study. We have not made specific plans to disseminate the results directly to study participants, as our focus is on synthesising existing research findings for academic and clinical stakeholders.

DISCUSSION

To the best of our knowledge, this is the most up-to-date and comprehensive review focusing on current studies targeting treatments specifically for IED. Unlike individuals influenced occasionally by general aggressiveness or impulsiveness, individuals with IED exhibit more complex symptoms and endure the disorder for a longer period. However, the management of IED presents a significant challenge due to its complex aetiology and the variability in patient response to treatment. Therefore, this meta-analysis aims to synthesis existing research on the psychological and pharmacological treatments of IED to identify the most effective therapeutic modalities. By adopting a protocol that meticulously compares the efficacy of treatments against control conditions, this study addresses a critical gap in the literature and provides a systematic evaluation of current interventions.

The findings of this meta-analysis are expected to highlight the relative strengths of CBT, which remains a cornerstone in the psychological treatment of IED. Our results are expected to align with existing literature that consistently supports CBT's effectiveness in managing IED symptoms. Studies such as Coccaro *et al* and McCloskey *et al* have shown significant reductions in aggressive outbursts through CBT interventions. The structured approach of CBT, with its emphasis on understanding and modifying thought patterns and behaviours, is anticipated to be validated as an effective intervention. Moreover, the analysis may also reveal the potential of pharmacological treatments, such as SSRIs, to manage the symptoms of IED, particularly in reducing the frequency and intensity of explosive outbursts. The meta-analysis is also expected to shed light on how these comorbid conditions, such as mood and anxiety disorders, influence the treatment trajectory of IED. This insight can guide clinicians in creating comprehensive, personalised treatment plans that address the multifaceted nature of the disorder.

The limitations of the current meta-analysis will also be acknowledged, including potential publication bias and the inclusion of studies with diverse methodologies. For instance, one of the significant limitations of this meta-analysis and systematic review is the relatively small number of studies included. The limited number of studies may contribute to high heterogeneity, making it challenging to draw consistent and reliable conclusions about the effectiveness of the interventions studied. The limited number of studies qualified was partially due to the fact that IED has only relatively recently been recognised as a distinct psychiatric disorder, and its diagnostic criteria have evolved over time. However, awareness and understanding of IED among clinicians and researchers have increased only in recent years, leading to a gradual rise in focused research. Such limitations underscore the need for a cautious interpretation of the results and suggest areas for improvement in future research.

In summary, the findings of this study corroborate existing knowledge in the field of IED treatment, the impact of comorbid conditions, and the methodological challenges faced in research. By providing a comparative analysis of psychological and pharmacological treatments, this study aims to inform evidence-based clinical practices and stimulate further research to enhance the quality of care for individuals with IED. To improve

treatment for IED, there needs to be increased awareness, better diagnostic tools and more dedicated research into the specific mechanisms of the disorder. Future research should focus on tailoring the development of integrated treatment models to improve treatment outcomes for individuals with IED.

Contributors FL was instrumental in formulating the research questions and objectives, developing the methodology for the systematic search and data extraction and designing the analysis strategy. FL drafted the initial protocol manuscript and is the guarantor of the review. XY contributed extensively to the development of the selection criteria, the risk of bias assessment strategy and provided a substantial contribution to the planning of the data synthesis, including statistical methodology. XY also participated in the drafting and critical revision of the protocol manuscript, adding intellectual content and revising methodology for clarity and accuracy. Both authors FL and XY reviewed and approved the final version of the protocol manuscript and agreed to be responsible for all aspects of the work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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Search terms

IED: Intermittent Explosive Disorder OR IED OR Impulsive

Treatment: Treatment OR Intervention OR Therapy OR Interve*

Pharmacological: drug OR Pharma* OR Psychopharm* OR Antidepressants OR Mood stabilizers

Psychological: CBT OR Cognitive Behavioral Therapy OR Anger management*

Others: Randomized controlled trial OR Randomised controlled trial OR RCT OR Integrated treatment

Exemplary search results from Ovid

APA PsycInfo <1806 to December Week 3 2023>

Embase Classic+Embase <1947 to 2023 Week 51>

Global Health Archive <1910 to 1972>

Global Health <1973 to 2023 Week 51>

Ovid MEDLINE(R) <1946 to December Week 4 2023>

1 (Intermittent Explosive Disorder or IED or Impulsive).mp. [mp=ti, ab, tx, ct, sh, hw, id, tc, ot, tm, mf, tn, dm, dv, kf, fx, dq, cw, bt, nm, ox, px, rx, an, ui, sy, ux, mx]95562

2 (Treatment or Intervention or Therapy or Interve*).mp. [mp=ti, ab, tx, ct, sh, hw, id, tc, ot, tm, mf, tn, dm, dv, kf, fx, dq, cw, bt, nm, ox, px, rx, an, ui, sy, ux, mx] 32840737

3 (drug or Pharma* or Psychopharm* or Antidepressants or Mood stabilizers).mp. [mp=ti, ab, tx, ct, sh, hw, id, tc, ot, tm, mf, tn, dm, dv, kf, fx, dq, cw, bt, nm, ox, px, rx, an, ui, sy, ux, mx] 26570520

4 (CBT or Cognitive Behavioral Therapy or Anger management*).mp. [mp=ti, ab, tx, ct, sh, hw, id, tc, ot, tm, mf, tn, dm, dv, kf, fx, dq, cw, bt, nm, ox, px, rx, an, ui, sy, ux, mx] 170398

5 (Randomized controlled trial or Randomised controlled trial or RCT or Integrated treatment).mp. [mp=ti, ab, tx, ct, sh, hw, id, tc, ot, tm, mf, tn, dm, dv, kf, fx, dq, cw, bt, nm, ox, px, rx, an, ui, sy, ux, mx] 2129647

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Exemplary search results from CENTRAL

"Intermittent Explosive Disorder" AND (treatment OR intervention OR therapy) AND (pharmacological OR drug OR psychopharmacology OR antidepressants OR mood stabilizers) AND (psychological OR CBT OR "Cognitive Behavioral Therapy" OR "anger management") AND ("Randomized controlled trial" OR RCT OR "integrated treatment")

932 results for **"Intermittent Explosive Disorder OR IED OR Impulsive"** anywhere and **"Treatment OR Intervention OR Therapy OR Interve*"** anywhere and **"drug OR Pharma* OR Psychopharm* OR Antidepressants OR Mood stabilizers"** anywhere and **"CBT OR Cognitive Behavioral Therapy OR Anger management*"** anywhere and **"Randomized controlled trial OR Randomised controlled trial OR RCT OR Integrated treatment"** anywhere