Systematic review and meta-analysis: Pharmacological and nonpharmacological interventions for disruptive mood dysregulation disorder

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Research Article

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Abstract

Background

Disruptive mood dysregulation disorder (DMDD) is a relatively new diagnostic approach that focuses on describing severe, non-episodic irritability and recurrent outbursts of emotional instability in adolescents.

Methods

This meta-analysis examined the efficacy of the available pharmacological and nonpharmacological interventions for DMDD. Literature searches were conducted in July 2023. To determine relevant papers, 330 abstracts were reviewed, and 39 articles were identified for full review. A random-effects model was used for the meta-analysis, and a subgroup analysis was used to assess the effects of study design and intervention type. Eleven studies were included (six pharmacological and five nonpharmacological).

Results

Despite high heterogeneity in effects (I^2=85%), we showed statistically significant improvement to irritability symptoms following intervention (standardized mean difference = 0.78, 95% confidence interval = 0.21–1.36, Z = 2.68, P□0.05). The subgroup analysis showed that, compared with randomized controlled trials (RCTs), participants in open trials showed significant improvement in irritability. Additionally, drug intervention significantly improved irritability compared to non-drug interventions. Atomoxetine, optimized stimulants, or stimulants combined with other drugs and behavioral therapy effectively improved irritability. However, large-sample RCTs are needed to explore DMDD treatment without potential influencing factors.

Conclusion

In conclusion, treatment strategies for persistent non-periodic irritability in youths with DMDD are diverse, and because of DMDD symptoms and its intersection with other diseases, it is necessary to combine multiple treatment strategies.

1. Background

Disruptive mood dysregulation disorder (DMDD) is a relatively new diagnostic approach that addresses severe non-episodic irritability and recurrent outbursts of emotional frustration in adolescents. DMDD replaced the severe mood dysregulation diagnosis, which included criteria for hyperarousal and was included in the depressive disorder category of The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [1]. Characteristic features include emotional outbursts occurring three or more times per week in adolescents aged 6–17, which can be expressed verbally or behaviorally (such

as aggression towards objects or physical attacks on others). These emotional outbursts are characterized by a duration or intensity that is not in line with the context of the situation and is developmentally inappropriate for the child. The emergence of DMDD can indeed help address the problem of over-diagnosing children with pathological irritability and explosive/angry temper as having bipolar disorder [2]. This misdiagnosis results from the symptoms of DMDD potentially resembling the emotional fluctuations observed in bipolar disorder. However, there is currently no clear gold standard for diagnosing DMDD, which leads to varying prevalence estimates. Different studies have employed varying methods and criteria, resulting in inconsistent estimations of disease rates. Adolescents with DMDD often have comorbidities with other mental disorders, the most common being oppositional defiant disorder (ODD), anxiety/mood disorder (MD), and post-traumatic stress disorder (PTSD) [3]. Most adolescents with DMDD may have already received treatment for their comorbid mental disorders, but their irritable mood has not been significantly controlled. The treatment of DMDD is complex and varied. In terms of medication, stimulants have broad applicability in treating irritability and aggression [4]. Nonpharmacological interventions, such as cognitive-behavioral and family therapies, are also considered beneficial treatment approaches for individuals with DMDD and their families [5]. However, the multitude of treatment methods and their varying effectiveness make it difficult to establish objective, evidence-based practices for the clinical management of DMDD. Existing guidelines for DMDD treatment are limited. Therefore, the aim of this study was to identify feasible and effective treatment methods through a comprehensive review and meta-analysis of current pharmacological and nonpharmacological interventions for DMDD.

2. Methods

2.1 Search strategy

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for preferred reporting items [6]. This protocol has been registered with the International Prospective Register of Systematic Reviews under the pre-registration protocol ID CRD42023433662 (PROSPERO, 2023). We conducted a search of four databases: PubMed, Embase, the Cochrane Controlled Trials Register, and the Web of Science Core Collection. Other search sources included ClinicalTrials.gov. Each database was searched from 2013 to 2023 using the following keywords: (disruptive mood dysregulation disorder OR DMDD) AND (treatmen* OR interventio* OR therap*).

2.2 Inclusion and exclusion criteria

The inclusion criteria consisted of prospective study reports (including randomized controlled trials [RCTs], non-controlled trials, and open trials) and retrospective study reports, with a language limit of English. The study population included adolescents who met the DSM-5 diagnostic criteria for DMDD and were under 18 years of age, regardless of race or sex. Interventions included any pharmacological, nonpharmacological, or combined treatment. The primary outcome measure was scores of irritability

before and after interventions or measures that substituted irritability, such as changes in disease severity before and after interventions. The original data content was a continuous variable. The exclusion criteria were as follows: (1) abstracts, conference papers, and posters; and (2) literature with incomplete information, individual cases, duplicate publications from the same study, unclear diagnoses, or incomplete clinical trials.

2.3 Literature screening

First, two reviewers independently screened the titles and abstracts of the articles based on the inclusion and exclusion criteria to identify relevant literature. Next, the authors obtained full articles and reviewed them independently to determine if they met the inclusion criteria. Discrepancies were resolved through discussion.

2.4 Data extraction

Two data extractors independently extracted the data using a predesigned form, including the title, first author's name, study design, publication year, disease type, sample size, outcome measures, follow-up time, dropout numbers during follow-up, and number of adverse events. For continuous outcome variables, data extraction included the mean change from baseline, standard deviation, and number of participants assessed at the endpoint for each outcome measure in each study. For dichotomous outcome variables, data extraction included the sample size for each group, number of dropouts, and number of adverse events. Discrepancies were resolved through discussion.

2.5 Quality evaluation of the included literature

The methodological quality of the included studies was assessed according to the risk assessment criteria for bias in RCTs in the Cochrane Handbook 5.0. This included: (1) inclusion of random sequence generation; (2) allocation concealment; (3) whether participants and implementers adopted the blind method; (4) whether the results evaluator adopted the blind method; (5) the integrity of the resulting data; (6) whether the research results were selectively reported; and (7) other sources of bias (such as early trial termination, and baseline inconsistency). These seven items were rated as "yes" (low bias), "no" (high bias), or "unclear" (lack of relevant information or uncertain bias) [7].

2.6 Statistical analysis

RevMan5.3 software was used to analyze the data included in the literature. According to Morris (2008), the pre- and post-intervention means and standard deviations were used to calculate the standardized mean difference (SMD) for all measures of aggression [8]. For RCTs, control group data was used as pre-intervention, and intervention group data was used as post-intervention to calculate the SMD for all intervention studies, regardless of the intervention type (i.e., pharmacological, nonpharmacological, or combination treatment). A random-effects model was used for analysis, as recommended, and a sensitivity analysis was conducted to evaluate the stability of the results. If significant heterogeneity was observed, a subgroup analysis was performed.

2.7 Primary outcome measure(s)

(1) The Affective Reactivity Index (ARI) is a self- and parent-reported dimension of irritability designed to measure emotional reactivity in individuals aged 7–18 years old. This scale provides information about anger reaction thresholds as well as the frequency and duration of anger emotions/behaviors [9]. Other measures used to provide information on irritability included the Swanson, Nolan and Pelham-IV (SNAP-IV) Irritability Index [10] or Emotional Symptoms Questionnaire (MSQ-7) [11].

(2) The overall impression or severity scale of DMDD was used for patients without irritability-related symptoms, including the Clinical Global Impression Scale (CGI) [12] or Global Assessment Scale for Children (CGAS) [13].

(3) When multiple measurements were reported, those evaluated by certified clinicians took precedence over those evaluated by patients. In cases in which several post-treatment time points were reported, the last treatment time point was selected for analysis. Whether calculated from pre-intervention to post-intervention or between the intervention and control groups, the effect size was such that the reduction in irritability was always directly proportional.

3. Results

3.1 Literature search results

Through a preliminary search, 542 relevant studies were identified, and 11 were finally included. Figure 1 shows a PRISMA flowchart of this process.

3.2 Basic features of the included literature

Literature quality evaluation was conducted only for the included RCTs. The details are shown in Fig. 2.

3.3 Basic characteristics of the literature

Eleven studies were included in the analysis, consisting of four RCTs and seven non- RCTs with 286 participants in total. Among the 11 studies, four included 107 participants with a diagnosis of DMDD combined with attention deficit hyperactivity disorder (ADHD), while the remaining seven studies included 179 participants primarily diagnosed with DMDD; however, some participants had comorbid diagnoses (mainly anxiety disorders [47%], ADHD [37%], and ODD [40%]). Regarding intervention type, six studies focused on pharmacological interventions, and five focused on nonpharmacological interventions. Pharmacological interventions included stimulants, aripiprazole combined with methylphenidate (MPH), citalopram combined with MPH, and atomoxetine (ATX). Nonpharmacological interventions mainly included Parenting Management Training (PMT), Interpretation Bias Training (IBT), Exposure-Based Cognitive Behavioral Therapy (CBT), Interpersonal Psychotherapy for Mood and Behavior Dysregulation (IPT-MBD), and Dialectical Behavior Therapy for Children (DBT-C). Before the intervention, 27% of the participants with DMDD used stimulants, 22% used antipsychotic drugs, 17% used antidepressant drugs, 9% used antiepileptic drugs, and 3% used mood stabilizers. In this study, five

tests used the ARI scale to measure irritability, whereas the remaining tests used the CGI-I, SNAP-IV, and CGAS scales. Basic characteristics of the included literature are presented in Table 1.

Table 1
Overview of Literature Characteristics

Report	Intervention type	Subjects(N)	Age range, y	Females(%)	Country/ race/ethnicity distribution (%)	Design
Baweja et al., 2016 [14]	CNS Stimulants	38	7–11	11(28)	USA: 26.3 racial/ethnic minority	Open trial
Benarous et al., 2020 [15]	ATX	6	10–14	2(33)	France	Open trial
Byrne and Connon, 2021 [16]	PMT	12	6–12	2(16.6)	Ireland	Open trial
Haller et al., 2022 [17]	IBT	22 + 22	9–14	19(43)	USA: 89 White, 14 Hispanic	RCT
Kircanski et al., 2018 [18]	CBT	10	9–15	4(40)	USA: race/ethnicity not provided	Open trial
Miller et al., 2018 [19]	IPT-MBD	10 + 9	12–17	8(42)	USA: 57.9 White, 10.5 Hispanic	RCT
Ozyurt et al., 2017 [20]	MPH	12	13	0	Turkey	Open trial
Pan et al., 2018 [21]	ARI + MPH	29	7–17	5(15.1)	China Taiwan	Open trial
Perepletchikova et al., 2017 [22]	DBT-C	21 + 22	7–11	19(44)	USA: 76.7 White, 11.6 Hispanic	RCT
Towbin et al., 2020 [23]	MPH + CTP/PBO	23 + 26	7–15	16(32.7)	USA: 79.6 White, Hispanic not reported	RCT
Winters et al., 2018 [24]	MPH	22	9–15	7(31)	USA: 31.8 White, ethnicity not reported	Open trial

Report	Intervention type	Subjects(N)	Age range, y	Females(%)	Country/ race/ethnicity distribution (%)	Design

Note: For any study conducted outside of the United States, the country is listed without race/ethnicity information, as this was typically not provided. ATX = atomoxetine; PMT = Parenting Management Training; IBT = Interpretation Bias Training; CBT = Cognitive Behavioral Therapy; IPT-MBD = Interpersonal Psychotherapy for Mood and Behavior Dysregulation; DBT-C = Dialectical Behavior Therapy for Children; MPH = Methylphenidate; ARI = Aripiprazole; CTP = Citalopram; PB0 = placebo; RCT = randomized controlled trial

<Insert Table 1 here>

3.4 Data analysis

3.4.1 Primary outcome measure

After heterogeneity testing, the 11 literature sources used in this study showed I^2=85% and a Q-test P-value less than 0.1, indicating significant heterogeneity among the selected literature sources. Therefore, we performed a random-effects meta-analysis. The results of the random-effects meta-analysis indicated a statistically significant difference between the overall combined effect of the intervention on irritability from pre-intervention to post-intervention compared to zero (SMD = 0.78, 95% CI = 0.21–1.36, Z = 2.68, P□0.05). The sensitivity analysis found that none of the studies had a strong impact on the results of the research. The details are shown in Fig. 3.

3.4.2 Subgroup analysis of different test methods

Based on the reports of the included studies, studies were divided into RCTs and open trials for the subgroup analysis. The I^2 values for the two types of trials were 92% and 76%, respectively, indicating that there was still high heterogeneity within each group and that this subgroup analysis could not explain the source of heterogeneity.

The SMD for the open trials was 0.83 (95% CI:0.24–1.41, P = 0.006), indicating a statistically significant difference. However, for RCTs, the SMD was 0.67 (95% CI:-0.69-2.03, P = 0.34), indicating that the difference was not statistically significant. The details are presented in Fig. 4.

3.4.3 Subgroup analysis of different interventions

Based on the included literature reports, the studies were divided into subgroups of pharmacological and nonpharmacological interventions for subgroup analysis. The I^2 values of the two intervention methods were 88% and 72%, respectively, indicating that there was still high heterogeneity within the two groups and that this subgroup analysis could not explain the source of heterogeneity. The SMD for drug treatment was 1.22 (95% CI:0.36–2.08, P = 0.005), indicating a statistically significant difference. The

SMD for non-drug treatment was 0.29 (95% CI: -0.37-0.95, P = 0.39), indicating that the difference was not statistically significant. The details are shown in Fig. 5.

3.4.5 Tolerability and acceptability

Tolerability and acceptability were defined differently between the studies and were not sufficiently homogeneous to be considered in the quantitative meta-analyses. Across all studies, the highest discontinuation rate for the treatment of DMDD was reported by Ozyurt et al. (2017). Eleven of the 12 patients reported adverse effects with MPH and eventually discontinued use. Another study on the effects of MPH treatment indicated that they were small and well-tolerated. The most common adverse effects were decreased appetite and vomiting.

4. Discussion

This systematic review and meta-analysis investigated the efficacy of pharmacological and nonpharmacological treatments for persistent irritability in adolescents with DMDD. Despite the high heterogeneity among the studies, it was found that some studies demonstrated a certain therapeutic effect on improving irritability, while others showed no obvious improvement, or even exacerbated, irritability. Therefore, this study provides a reference for treating DMDD. Subgroup analysis (pharmacological/nonpharmacological, RCT/open trial) did not significantly explain the differences in effect size between the total sample and any clinical subgroup sample. This may be due to both the positive and negative effects of pharmacological or nonpharmacological treatment and RCT or open trials on the effective treatment of irritability. Open trials and pharmacological interventions indicated statistically significant effects on irritability improvement, whereas RCTs and nonpharmacological interventions demonstrated no statistically significant effects on irritability reduction. This may be because psychological factors in the participants of open trials and the selection and evaluation bias of the researchers potentially influenced the intervention results [25]. Pharmacological treatments may be superior to nonpharmacological treatments because drugs can directly produce an effect and work faster than nonpharmacological treatments. At the same time, nonpharmacological treatments may progress more slowly, demand more time, and their therapeutic effects may be subject to greater subjectivity.

4.1 Pharmacological treatment

In all studies, ATX appeared to be the most effective in improving irritability. However, the study on the treatment of DMDD with ATX had a sample size of six cases and was an open-label trial, which may have affected the reliability of the results. Stimulants are the most commonly used drugs for the treatment of irritability and aggression, and they have been widely used to reduce aggressive behaviors in adolescents with ADHD. However, a recent meta-analysis found that different types of stimulants could either increase or decrease irritability in adolescents with ADHD [26]. Therefore, the effect of stimulants on irritability in adolescents with DMDD remains controversial. This study found that some adolescents with DMDD experienced a reduction in irritability after using stimulants, as demonstrated by Baweja et al.

(2016), who found that adjusting the central nervous system stimulant to an optimal dose improved irritability. However, Ozyurt et al. (2017) and Winters et al. (2018) found that using MPH alone for the treatment of adolescents with DMDD did not improve irritability, and in some cases, even increased irritability. In the study by Ozyurt et al. (2017), all participants ultimately had to stop taking the medication, owing to poor tolerability. In the other two studies, which also used stimulants as an intervention, Pan et al. (2018) combined stimulants with aripiprazole, and Towbin et al. (2020) combined stimulants with citalopram. Both studies reported a significant decrease in irritability.

It is possible that irritable adolescents are at higher risk of developing depression and anxiety symptoms [27]. Two open-label trial results on the impact of antidepressant drugs on irritability, opposition, and aggression in children and adolescents suggested that selective serotonin reuptake inhibitors (SSRIs) were effective in treating irritability associated with adolescent depression [28, 29]. Therefore, the use of ATX or other stimulants in combination with citalopram may improve irritability by controlling internalized emotions.

Risperidone and Aripiprazole are the only medications approved by the FDA for the treatment of symptoms such as irritability, aggressive behavior, and self-injury in patients with autism spectrum disorder (ASD) [30]. Therefore, the therapeutic effectiveness of stimulants in treating irritable moods in adolescents with DMDD requires further validation through additional clinical trials. Moreover, individualized dosing and treatment plans should be adjusted when administering stimulant therapy, and comprehensive interventions incorporating antipsychotic or antidepressant medications may be more effective in achieving better treatment outcomes.

4.2 Nonpharmacological Treatment:

In a preliminary pilot trial, Kircanski et al. (2018) found that after CBT treatment, the severity of irritability scores in adolescents with DMDD showed a significant decrease. Perepletchikova et al. (2017) found that DBT-C had significant therapeutic effects in reducing irritability in adolescents, and that both parents and children found it to be more acceptable and satisfactory. CBT is a recognized treatment method for childhood depression and anxiety disorders [31], which may reduce irritable moods in adolescents with DMDD through emotion regulation and improvement in interpersonal relationships. DBT-C is a form of CBT that is more appropriate for children and adolescents. It is based on the principles and techniques of adult DBT, with personalized adjustments and changes to the specific needs of younger people. DBT-C focuses not only on family therapy and parental involvement, but also on the social skills of children and adolescents to help them communicate better with their peers and build healthy relationships [32]. In particular, DBT-C has shown initial efficacy and feasibility in the treatment of adolescents with DMDD.

A preliminary randomized trial by Miller et al. (2018) evaluated the feasibility and acceptability of IPT-MBD as a treatment for adolescents with DMDD compared to treatment as usual (TAU). The study found that IPT-MBD was feasible and acceptable for both parents and adolescents, and it had some therapeutic efficacy. IPT-MBD is effective in treating and preventing psychological problems by reducing

outbursts and irritability while enhancing interpersonal communication, problem-solving skills, and emotional awareness [33].

A study by Byrne and Connon (2021) found that although the ARI-P did not significantly decrease with PMT, other measurement indicators based on parental reports showed a significant reduction in children's aggressiveness and behavioral problems and an increase in prosocial behavior. PMT teaches parents effective parenting skills to improve family relationships, promote positive behaviors in children, and reduce problematic behavior [34].

Haller et al. (2022) suggested that anger and its associated structures are related to a biased form of facial-emotion labeling, which can be altered through cognitive training. They attempted to change the interpretation of ambiguous emotional faces from anger to happiness through training. Although the anger scores of irritable adolescents improved after training, there was an increase in anger scores at the 2-week follow-up. Furthermore, there was no significant difference in anger improvement between the active and sham IBT groups. Therefore, this method is not recommended.

4.3 Limitations

The first limitation of this study is that structured interviews and questionnaires specifically developed for diagnosing DMDD are still in their early stages. Therefore, there are currently no recognized standards or a widespread consensus regarding the clinical assessment of DMDD [35]. For example, Copeland et al. (2013) used structured psychiatric interview data in a study of community adolescents and reported three-month prevalence rates of DMDD ranging from 0.8–3.3% [36]. Another representative large-scale study conducted by Althoff et al. (2016) used strict DMDD criteria and reported a prevalence of 0.12% in a sample of adolescents [37]. The variation in the prevalence rate of DMDD in different studies may have an impact on the inclusion criteria for various trials, thus affecting the accuracy of the trial results. Second, although various scales and measurement methods have been used in treatment studies of DMDD and have provided some clinical utility in monitoring symptoms, the inclusion of different assessment tools among the trials included in this study led to different outcome measures, which contributed to the heterogeneity of the results. Furthermore, the current lack of a gold standard for the treatment of DMDD has led to variations in treatment methods based on individual and professional differences. Almost every intervention measure in the included studies differed, which also had an impact on the heterogeneity of the results. Finally, most adolescents with DMDD have comorbidities, and different medications may be used to treat different comorbid conditions. These influencing factors can affect the heterogeneity of the results.

5. Conclusion

Currently, there is limited research on medication treatment for adolescents with DMDD, and most studies are open-label, which means that there may be some inherent limitations and uncertainties. Although ATX has been shown to be effective, larger RCTs are needed to evaluate its efficacy and safety in the treatment of DMDD more accurately. Stimulants may have some potential efficacy in treating

DMDD, especially when used in combination with atypical antipsychotic drugs (such as aripiprazole) or antidepressant medications (such as sertraline), which may be considered an option for treating DMDD. However, the use of stimulants alone to treat DMDD in adolescents is not recommended due to poor efficacy and tolerability. CBT, especially DBT-C, has shown preliminary therapeutic effectiveness and feasibility for the treatment of DMDD. Additionally, although PMT holds promise for treating DMDD, the current results are exploratory and should not be considered as empirical support for this specific population. IPT-MBD holds promise as a potentially effective psychosocial intervention for clinically impaired youths with DMDD, and further research is warranted in larger-scale randomized trials. The IBT RCT did not find significant differential improvements in the clinical outcomes of adolescents with DMDD, and further refinement is needed before it can be recommended. There are many diagnostic and treatment options for DMDD; however, there is currently no consensus on the optimal treatment approach. In summary, the treatment strategies for DMDD are diverse because of the symptoms of DMDD and their overlap with other disorders; therefore, the treatment of DMDD requires a combination of multiple strategies. In the future, larger-scale RCTs are needed to explore the treatment of DMDD while excluding potential confounding factors. The first large-scale RCT with ATX should investigate the improvement of irritability in adolescents following treatment. The use of stimulants in combination with atypical antipsychotics (such as aripiprazole) or antidepressants (such as citalopram), and stimulants in combination with other antidepressant classes (such as sertraline, fluvoxamine, etc.), can then be assessed to compare whether there is a better effect on improving irritability in adolescents. Finally, the combination of drug therapy with effective non-drug therapy, such as DBT-C or PMT combined with ATX or stimulants, should be evaluated as an effective treatment for DMDD.

Abbreviations

Disruptive mood dysregulation disorder (DMDD), randomized controlled trials (RCTs), Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), oppositional defiant disorder (ODD), mood disorder (MD), post-traumatic stress disorder (PTSD), Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), standardized mean difference (SMD), Affective Reactivity Index (ARI), Emotional Symptoms Questionnaire (MSQ-7), Clinical Global Impression Scale (CGI), Global Assessment Scale for Children (CGAS), Swanson, Nolan and Pelham-IV (SNAP-IV), attention deficit hyperactivity disorder (ADHD), atomoxetine (ATX), methylphenidate (MPH), Parenting Management Training (PMT), Interpretation Bias Training (IBT), Exposure-Based Cognitive Behavioral Therapy (CBT), Interpersonal Psychotherapy for Mood and Behavior Dysregulation (IPT-MBD), Dialectical Behavior Therapy for Children (DBT-C), selective serotonin reuptake inhibitors (SSRIs), autism spectrum disorder (ASD) treatment as usual (TAU)

Declarations

The authors declare that they have no financial or personal relationships with other people or organizations that constitute a conflict of interest.

Ethical Approval and Consent to participate

None

Availability of date

None

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

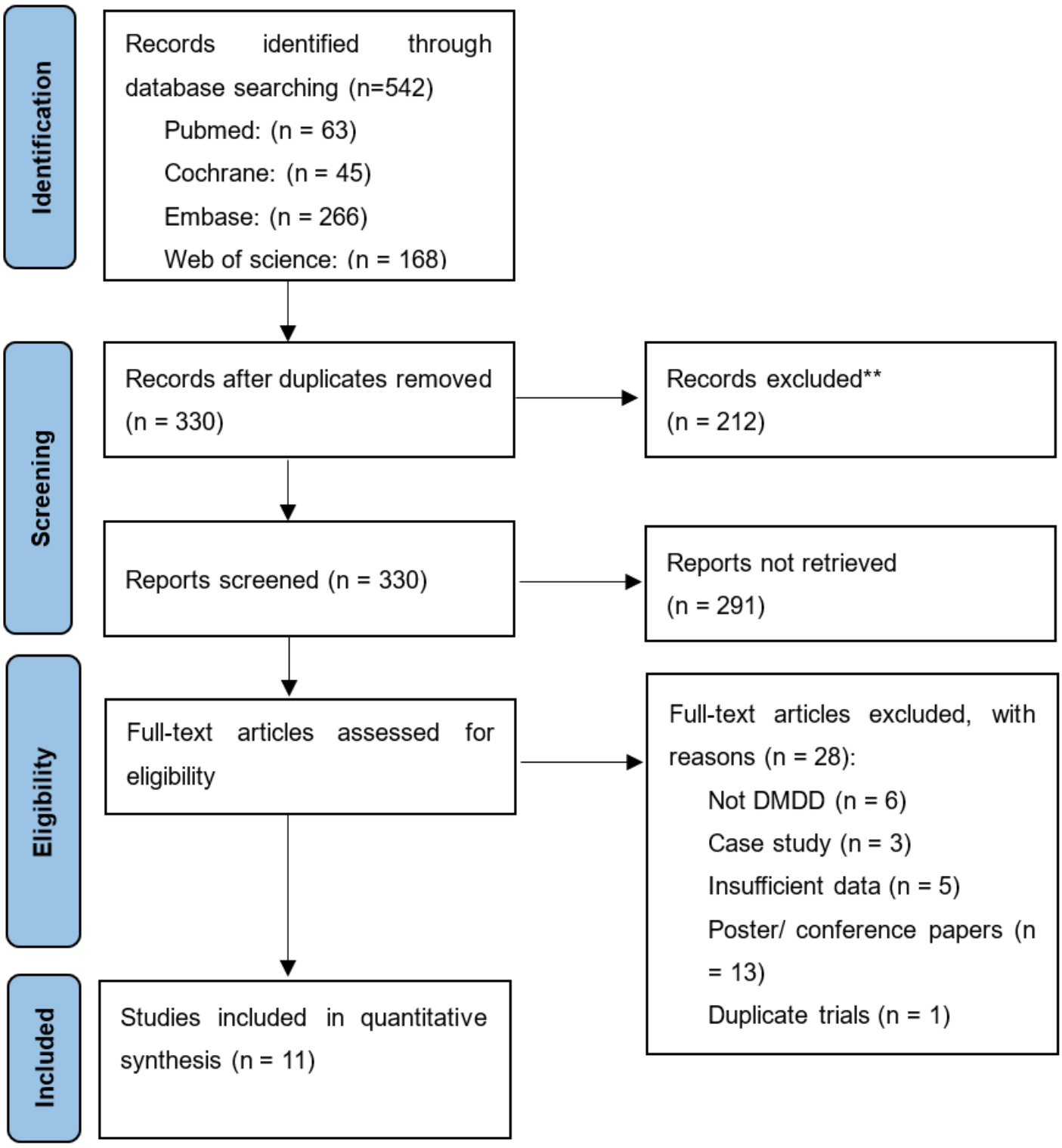

Figure 1

PRISMA flowchart of this process

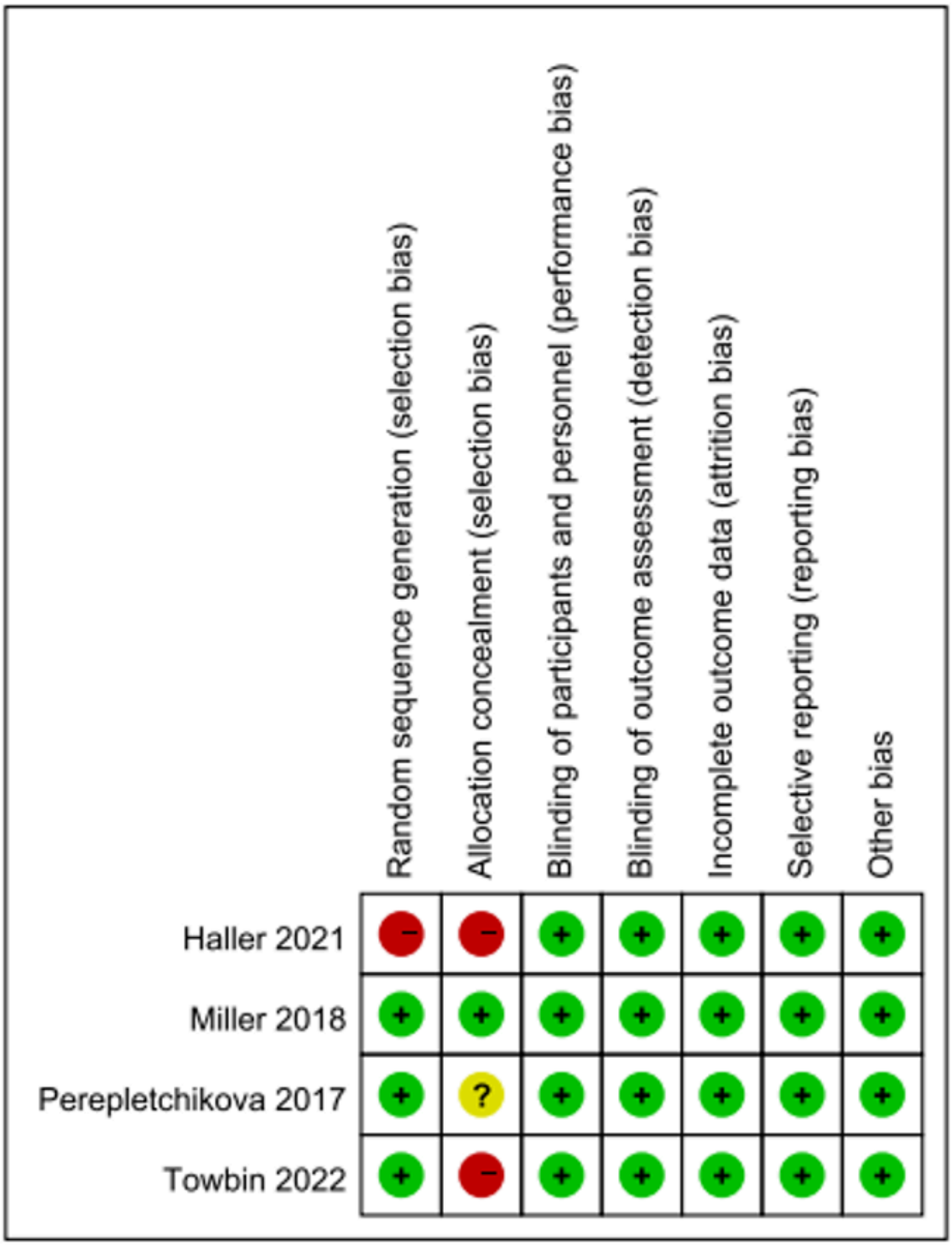

Figure 2

Literature quality

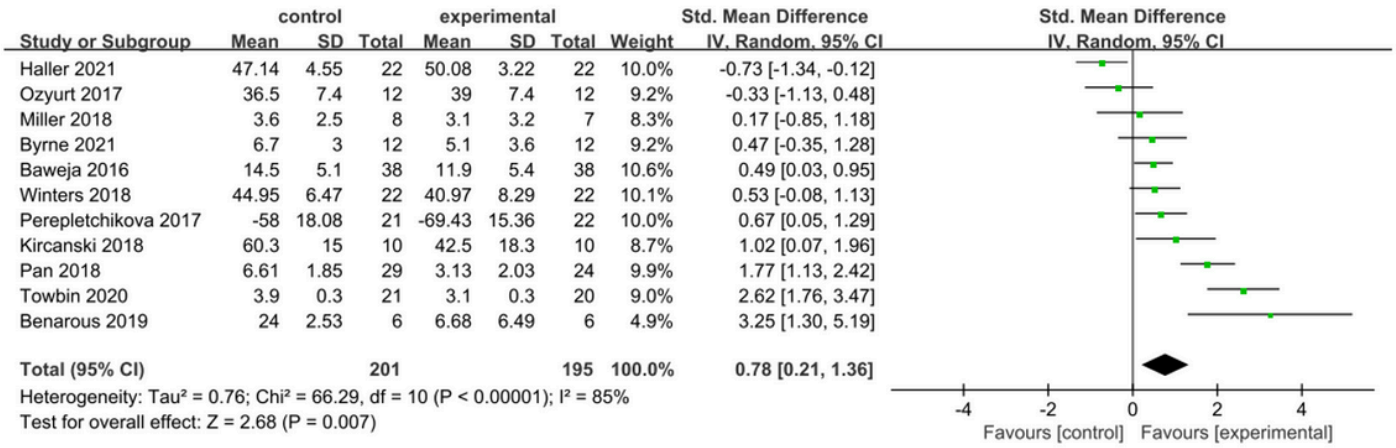

Figure 3

Primary outcome measure

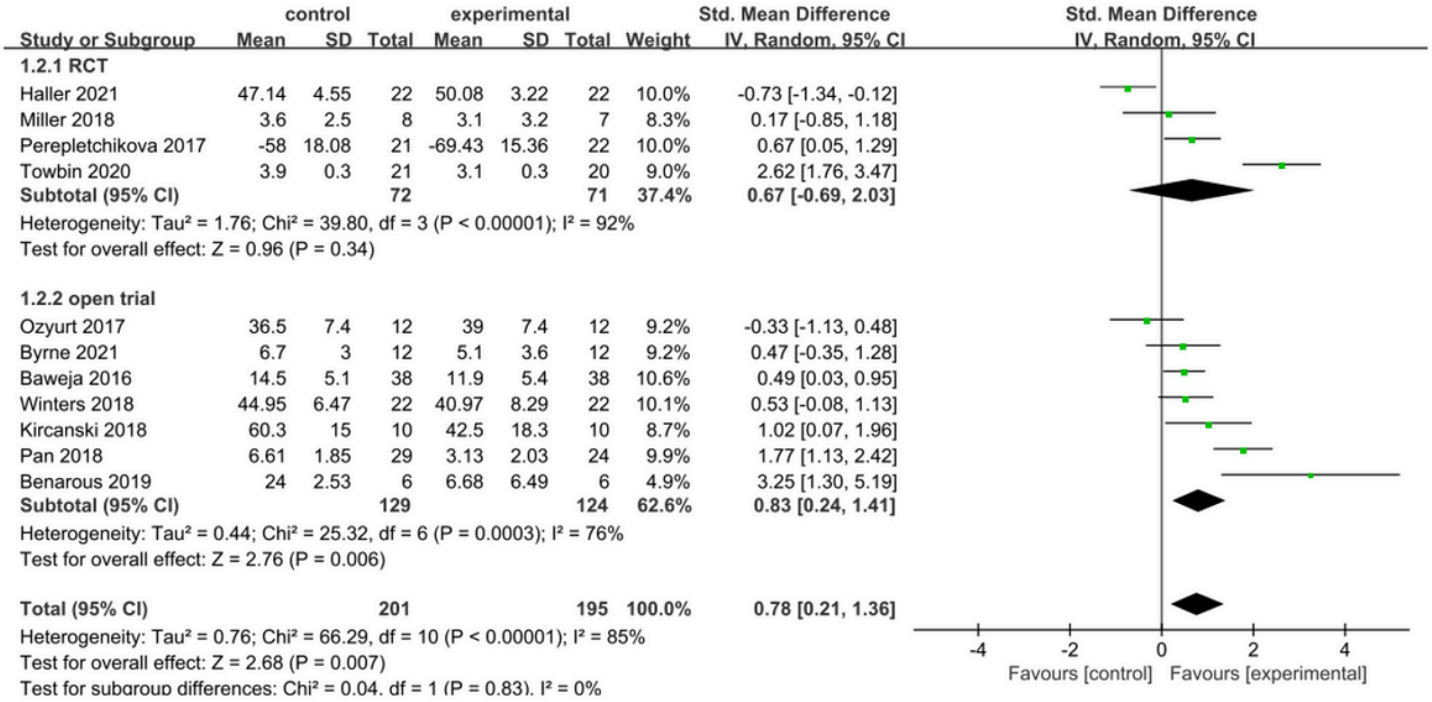

Figure 4

Subgroup analysis of different test methods

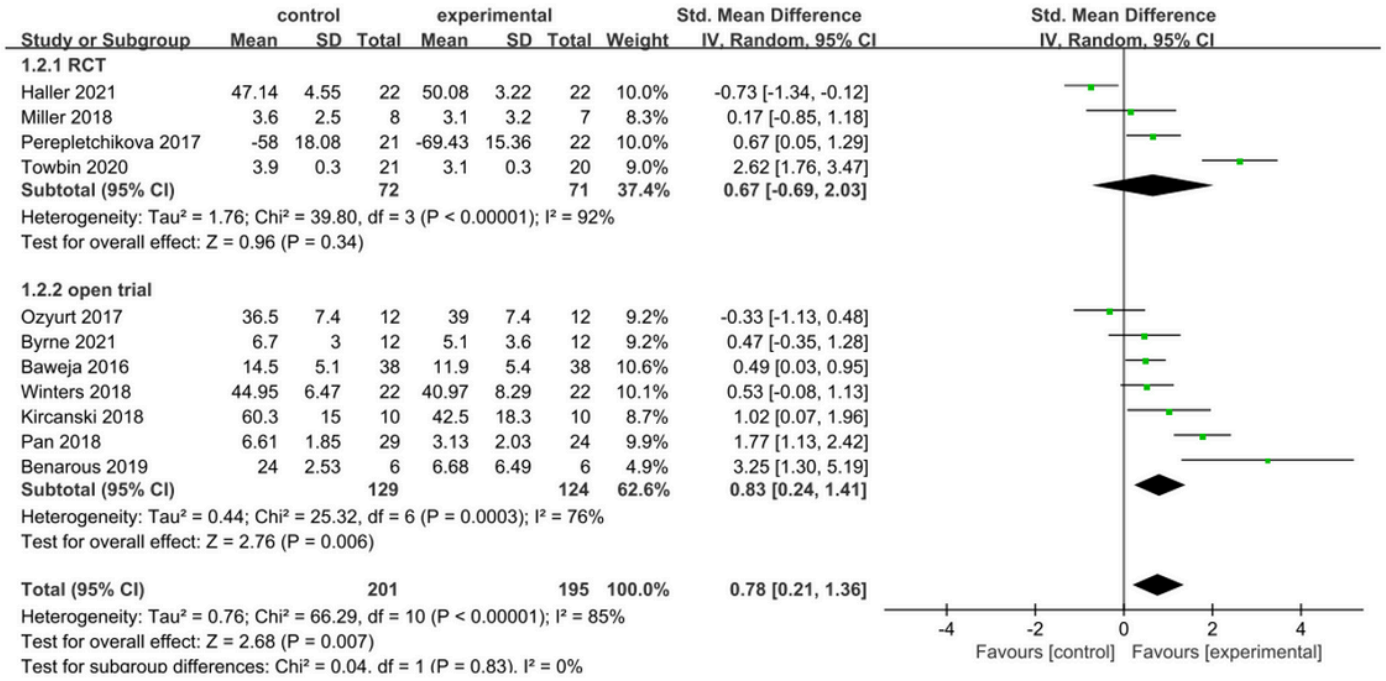

Figure 5

Subgroup analysis of different interventions