Efficacy and acceptability of pharmacological, psychosocial, and brain stimulation interventions in children and adolescents with mental disorders: an umbrella review

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Top-tier evidence on the safety/tolerability of 80 medications in children/adolescents with mental disorders has recently been reviewed in this journal. To guide clinical practice, such data must be combined with evidence on efficacy and acceptability. Besides medications, psychosocial interventions and brain stimulation techniques are treatment options for children/adolescents with mental disorders. For this umbrella review, we systematically searched network meta-analyses (NMAs) and meta-analyses (MAs) of randomized controlled trials (RCTs) evaluating 48 medications, 20 psychosocial interventions, and four brain stimulation techniques in children/adolescents with 52 different mental disorders or groups of mental disorders, reporting on 20 different efficacy/acceptability outcomes. Co-primary outcomes were disease-specific symptom reduction and all-cause discontinuation (“acceptability”). We included 14 NMAs and 90 MAs, reporting on 15 mental disorders or groups of mental disorders. Overall, 21 medications outperformed placebo regarding the co-primary outcomes, and three psychosocial interventions did so (while seven outperformed waiting list/no treatment). Based on the meta-analytic evidence, the most convincing efficacy profile emerged for amphetamines, methylphenidate and behavioral therapy in ADHD; aripiprazole, risperidone and several psychosocial interventions in autism; risperidone and behavioral interventions in disruptive behavior disorders; several antipsychotics for schizophrenia spectrum disorders; fluoxetine and interpersonal psychotherapy for depression; aripiprazole for mania; fluoxetine and group cognitive behavioral therapy (CBT) for anxiety disorders; fluoxetine/selective serotonin reuptake inhibitors and CBT/exposure response prevention for obsessive-compulsive disorder; CBT for post-traumatic stress disorder; imipramine and alarm behavioral intervention for enuresis; behavioral therapy for encopresis; and family therapy for anorexia nervosa. Results from this umbrella review of interventions for mental disorders in children/adolescents provide evidence-based information for clinical decision making.

Key words: Children, adolescents, pharmacotherapy, psychotherapies, psychosocial interventions, brain stimulation, ADHD, autism, disruptive behavior disorders, efficacy, acceptability

Many mental disorders have an onset with clinically relevant manifestations in childhood or adolescence, followed frequently by a chronic illness course into adulthood1,2. Many disorders with an earlier onset are first diagnosed in adulthood, with a delay ranging for example from 6 to 8 years for mood disorders and from 9 to 23 years for anxiety disorders3. Due to their interference with attainment of biopsychosocial milestones, mental and neurodevelopmental disorders in children and adolescents are among the leading causes of global burden of disease and years lived with disability4. This situation makes the appropriate delivery of evidence-based and effective treatments for youth with mental disorders a key priority in the public health field.

Pharmacological, psychosocial and brain stimulation options are available for the management of many mental disorders in children and adolescents. However, for several of them, what should be considered the first line treatment strategy – based on efficacy, effectiveness, acceptability and tolerability/safety – remains uncertain.

A number of randomized controlled trials (RCTs) have been conducted to assess the efficacy, acceptability and tolerability of medications across different disorders in children and adolescents. The results from many of these RCTs have been pooled in pairwise meta-analyses (MAs) or network meta-analyses (NMAs)5–8. While most antidepressants outperform placebo to treat depression in adults9, most antidepressants have not been shown to be superior to placebo in children and adolescents with major depressive disorder7,10. Similarly, yet to a lower extent, antidepressants may not be as effective in children and adolescents with anxiety disorders as in adults11.

On the other hand, RCTs comparing psychosocial interventions with waiting list or no intervention control groups generally show a large effect size in youth with depression10 or anxiety12 disorders. Yet, when compared with placebo/sham interventions, most significant findings favoring psychosocial interventions vs. placebo disappear10,12. Effect sizes also vary according to design, blinding, patient selection (baseline severity) and choice of the control group13 in trials assessing combination treatments, whose superiority to monotherapies has not been consistently confirmed within and across disorders in children/adolescents.

Differences in inclusion criteria, outcomes, and a variety of features defining quality across MAs and NMAs limit the clinical value and impact of such a rich, yet complex body of evidence. Umbrella reviews may overcome these problems to some degree by taking the totality of the evidence from existing MAs and NMAs into account, and filtering top-tier meta-analytic estimates according to pre-established criteria. It is paramount to provide clinicians with structured and standardized summaries, translating the massive data into actionable clinical information.

To our knowledge, no umbrella review is available of the evidence from MAs and NMAs of RCTs on the efficacy and acceptability of pharmacological, psychosocial, and brain stimulation treatment options for the core symptoms and associated problems of the full range of mental disorders in children and adolescents. The present study aims to fill this gap, as previously done in this journal concerning the safety and tolerability of 80 pharmacological agents used for the management of child and adolescent mental disorders14.

We focused on disease-specific symptom reduction and treatment response as efficacy measures, and on measures of acceptability that could be compared across the three different treatment modalities, namely all-cause discontinuation and intolerability-related discontinuation. Following this approach, this umbrella review intends to provide practitioners with an evidence-based atlas of therapeutic tools to inform clinical decision making, where a balance needs to be struck between efficacy, acceptability/tolerability, and safety.

METHODS

Search, inclusion and exclusion criteria

This umbrella review followed an *a priori* protocol (available upon request). We conducted a systematic search in PubMed, PsycINFO, and Cochrane database up to January 9, 2021, using an exhaustive combination of key words (full search string available upon request). We also manually searched bibliographies of included meta-analyses. Two independent authors conducted title/abstract screening, full-text assessment, and data extraction into a pre-defined excel spreadsheet. A third author triple-checked extracted data, and resolved any conflict.

Included were: a) NMAs or MAs of RCTs, b) of *a priori* defined 48 psychotropic medications, 20 psychosocial interventions, and four brain stimulation interventions, c) in children and/or adolescents, d) with any of 52 *a priori* defined mental disorders, e) reporting on 20 *a priori* defined outcomes within a specific disorder. Exclusion criteria were: a) systematic reviews without meta-analysis, b) pooling of studies other than RCTs, c) interventions for other than pre-defined disorders/outcomes.

Whenever two NMAs or MAs reported on the same combination of disorder, intervention, comparison and outcome, we considered the comparison with more RCTs, the minimum being at least one direct comparison for NMAs.

Included disorders, interventions, and comparisons

Mental disorders of interest, as grouped in the ICD-1115, were: a) neurodevelopmental disorders (autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), disorders of intellectual development, developmental speech or sound disorders, developmental learning disorders, developmental motor coordination disorders), b) schizophrenia and other primary psychotic disorders (schizophrenia, schizoaffective disorder, schizotypal disorder, acute and transient psychotic disorder), c) catatonia, d) mood disorders (bipolar and related disorders, depressive disorders), e) anxiety or fear-related disorders (generalized anxiety disorder, panic disorder, agoraphobia, specific phobia, social anxiety disorder, separation anxiety disorder, selective mutism), f) obsessive-compulsive and related disorders (obsessive-compulsive disorder, body dysmorphic disorder, body-focused repetitive disorders), g) movement disorders (Tourette’s syndrome, other tic disorder), h) disorders specifically associated with stress (post-traumatic stress disorder (PTSD), complex PTSD, prolonged grief disorder, reactive attachment disorder, disinhibited social engagement disorder), i) dissociative disorders (dissociative neurological symptom disorder, dissociative amnesia, trance disorder, dissociative identity disorder), j) feeding and eating disorders (anorexia nervosa, bulimia nervosa, binge eating disorder, avoidant-restrictive food intake disorder, pica, rumination-regurgitation disorder), k) elimination disorders (enuresis, encopresis), l) disorders of bodily distress or bodily experience (bodily distress disorder, body integrity dysphoria), m) disorders due to substance use or addictive behaviors, n) impulse control disorders (pyromania, kleptomania, compulsive sexual behavior disorder, intermittent explosive disorder), o) disruptive behavior or dissocial disorders (oppositional defiant disorder, conduct disorder).

Interventions included pharmacological, psychosocial, and brain stimulation interventions.

Medications comprised antidepressants (bupropion, mirtazapine, nefazodone, vilazodone, desvenlafaxine, duloxetine, venlafaxine, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, clomipramine, desipramine, imipramine, nortriptyline, amitriptyline); antipsychotics (fluphenazine, haloperidol, molindone, trifluoperazine, amisulpride, aripiprazole, asenapine, clozapine, loxapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, thioridazine, ziprasidone); anti-ADHD medications (amphetamines, atomoxetine, clonidine, guanfacine, methylphenidate, modafinil); mood stabilizers (carbamazepine, lamotrigine, lithium, oxcarbazepine, topiramate, valproate); and others (oxybutynin, desmopressin).

Psychosocial interventions included behavioral therapy (BT), cognitive behavioral therapy (CBT), problem solving, dialectical behavioral therapy, family-based therapy, interpersonal psychotherapy (IPT), mentalization based therapy, psychodynamic psychotherapy, supportive therapy, social skills training (SST), acceptance and commitment therapy, mindfulness, eye movement desensitization and reprocessing (EMDR), narrative exposure therapy (NET), cognitive remediation therapy, cognitive training, parent-child interaction therapy (PCIT), play therapy, art therapy, and occupational therapy.

Brain stimulation interventions included transcranial magnetic stimulation, transcranial direct current stimulation, electroconvulsive therapy, and neurofeedback.

Comparators were labeled as active drug, active psychosocial intervention, treatment as usual (TAU)/low intensity psychosocial intervention, waiting list/no treatment, or placebo/sham.

Outcomes

Co-primary outcomes were disease-specific primary symptom reduction and all-cause discontinuation (“acceptability”).

Secondary continuous outcomes were measures of aggressive behavior, anxiety (other than anxiety disorders), cognition (other than ADHD), depressive symptoms (other than depressive episode/disorder), irritability, suicidal ideation, global illness severity, functioning (as defined by authors), and quality of life.

Secondary categorical outcomes were study-defined treatment response, remission, relapse, hospitalization, discontinuation due to inefficacy, discontinuation due to intolerability, suicide attempt, completed suicide, and death. When available, treatment estimates from clinicians, teachers, parents, and children/adolescents were considered separately.

Quality of evidence

The quality of MAs and NMAs was measured using A Measurement Tool for the Assessment of Multiple Systematic Reviews (AMSTAR)-PLUS)16,17 to quantify both the methodological quality of MAs and NMAs with the first 11 items (AMSTAR) and of included RCTs with six additional items (AMSTAR-Content).

Methodological quality was categorized into low (<4), medium (4-7), and high (>7). Content quality was categorized into low (<4), medium (4-6), and high (>6). The lowest score between methodological and content quality determined the overall MA or NMA quality.

Statistical analysis

We converted continuous non-standardized outcomes, such as weighted mean differences, to standardized mean differences (SMDs), and binary outcomes to odds ratio (ORs) with Comprehensive Meta-analysis (CMA), Version 318. We then calculated the mean SMD for the primary efficacy outcome across pharmacological, psychosocial, and brain stimulation interventions for each disorder against placebo/sham and for waiting list/no intervention, as well as for active controlled monotherapy and combination treatment studies, prioritizing clinician rating, followed by teacher, parent, and then subject-rated estimates. For treatment response, in case no data were available for the continuous primary efficacy outcome, we converted Ors to SMDs, using CMA.

Whenever data conversion was not possible, we kept the original effect sizes as reported. Whenever we included data from meta-analyses that used fixed-effects models, we recalculated the meta-analysis using random-effects models19. For consistent and easy comparison, we harmonized effect sizes as follows: SMD<0 favors intervention, OR/risk ratio (RR) <1 favors intervention for discontinuation, suicide or relapse, while OR/RR>1 favors intervention for response or remission.

RESULTS

Search results and literature coverage

The search process is described in Figure 1. Out of 5,231 initial hits, we assessed 910 MAs and NMAs at full text level. Of these, we excluded 806, with specific reasons (list available upon request). The list of all included MAs and NMAs is available in Table 1, also indicating the number of included RCTs and participants, as well as the methodological quality (AMSTAR score) together with the quality of included RCTs (AMSTAR-Content median score).

We ultimately included 14 NMAs and 90 MAs, reporting on 15 disorders or groups of disorders. For ADHD, we included three NMAs5,20,21 and 21 MAs22-42; for autism, one NMA43 and 21 MAs12,44–63 (including one focusing on comorbid anxiety disorders and autism)12; for depressive disorders, two NMA7,10 and seven MAs64–70; for obsessive-compulsive disorder, one NMA71 and six MAs72–77; for anxiety disorders, two NMAs11,78 and five MAs12,79–82 (plus two MAs specific on social anxiety disorder83,84); for enuresis, one NMA85 and six MAs86–91, for disruptive behavior/dissocial/conduct disorders, five MAs92–96 (plus one focusing on youth with comorbid ADHD)25; for eating disorders, one NMA97 and four MAs98–101; for schizophrenia spectrum disorders, three NMAs8,102,103 and two MAs104,105; for bipolar disorder, four MAs106–109; for tic disorder, two MAs110,111; for Tourette’s disorder, two MAs112,113; for encopresis, two Mas114,115; for developmental coordination disorder, one MA116; and for PTSD, one MA117.

Overall, 85.4% of *a priori* selected medications were covered for at least one of the two co-primary outcomes, which was the case for 55% of the psychosocial interventions, and 25% of the brain stimulation interventions. Moreover, 70% of *a priori* selected outcomes were covered across monotherapy medication treatments (anti-ADHD medications: 65%, antidepressants: 55%, antipsychotics: 40%, mood stabilizers: 25%), 80% across psychosocial interventions, and 20% across brain stimulation interventions.

Among monotherapy medication treatments with data on co-primary outcomes, those most covered by the literature were atomoxetine (11 outcomes), methylphenidate (9 outcomes), amphetamines and risperidone (8 outcomes), aripiprazole, fluoxetine, guanfacine, lurasidone, quetiapine (7 outcomes), and asenapine, clonidine, olanzapine, paliperidone, sertraline (6 outcomes). Monotherapy psychosocial interventions most covered by the literature were CBT (12 outcomes), BT (9 outcomes), PCIT (7 outcomes), and CBT-oriented (i.e. problem solving, CBT/BT, CBT/SST), psychodynamic-oriented (inc. IPT) family-based (i.e. family therapy and family-oriented) (6 outcomes). Among brain stimulation interventions, neurofeedback was the only modality with data that could be included in this umbrella review (4 outcomes).

Quality of included evidence

Among 14 NMAs of RCTs, the median AMSTAR score was 9.5 (interquartile range, IQR: 7-11), and the median AMSTAR-Content score was 4 (IQR: 2.75-5). The median overall quality score across all effect sizes was low in six NMAs (42.9%), moderate in six (42.9%), high in the remaining two (14.2%).

Among 90 MAs of RCTs, the median AMSTAR score was 9 (IQR: 7-10) and the median AMSTAR-Content score was 2 (IQR: 1-3). The median overall quality score across all effect sizes was low in 71 MAs (78.9%), moderate in 19 (21.1%), and high in none.

Across NMAs and MAs of RCTs of medications, the median AMSTAR quality score for individual ESs was 10 (IQR: 7-11), being low in 0.85%, moderate in 24.73%, and high in 74.41% of the NMAs/MAs, while the AMSTAR-Content median quality score was 4 (IQR: 3-5), being low in 30.06%, moderate in 58.64%, and high in 11.30%.

Across NMAs and MAs of RCTs of psychosocial interventions, the median AMSTAR quality score for individual ESs was 11 (IQR: 10-11), being low in none of the NMAs/MAs, moderate in 8.21%, and high in 91.79%, while the median AMSTAR-Content quality score was 2 (IQR: 1- 3), being low in 87.39%, moderate in 12.61%, and high in none.

Across brain stimulation interventions, the median AMSTAR quality score for individual ESs was 9 (IQR: 8-10), being low in none of the NMAs/MAs, medium in 16.67%, and high in 83.33%, while the median AMSTAR-Content quality score was 2 (IQR: 2-4), being low in 66.67%, moderate in 33.33%, and high in none.

Efficacy, acceptability and tolerability of pharmacological, psychosocial, and brain stimulation interventions

All results of this umbrella review are detailed in Tables 2-7, as well as in supplementary Tables, and supplementary Figures.

*ADHD*

Results for ADHD are shown in Tables 2, 6 and 7. Amphetamines, methylphenidate, desipramine and modafinil had the largest effect size for the primary efficacy outcome.

Focusing on the two best interventions, amphetamines had the largest effect size based on the clinician-rated primary efficacy outcome vs. placebo (large effect size), and were superior to placebo also regarding response (large effect size), aggressive behavior (large effect size), academic functioning (medium effect size), global illness severity (large effect size), and less discontinuation due to inefficacy (large effect size), without significant differences regarding all-cause discontinuation (“acceptability”) or discontinuation due to intolerability (see Table 2).

Methylphenidate had medium to large effect sizes regarding the primary efficacy outcome vs. placebo across different raters, and was superior to placebo regarding other-than-attention cognition broadly (small to medium effect size), global illness improvement (large effect size), quality of life (medium effect size), acceptability (small effect size), and less discontinuation due to inefficacy (medium effect size), without significant differences concerning discontinuation due to intolerability. The efficacy of methylphenidate was also confirmed in youth with comorbid intellectual disability (see Table 2).

Clonidine, guanfacine and atomoxetine were also effective regarding the primary efficacy outcome, but with less consistent results across raters. Among psychosocial interventions, social skills training improved the primary efficacy outcome and functioning (small to medium effect size); however, the control group was waiting list/no treatment. Only behavioral therapy outperformed placebo for response (small effect size), impact on global illness severity (small effect size), and acceptability (small effect size). Neurofeedback did not show any significant efficacy outcome, nor any difference emerged on acceptability (see Table 2).

Alpha-2 agonists were an effective augmentation strategy when added to stimulants vs. placebo (small effect size). Importantly, combined interventions, and specifically methylphenidate with parent training or with clonidine, and atomoxetine with parent training, showed large effect sizes regarding response vs. placebo. Additionally, behavioral therapy plus stimulants was superior both to behavioral therapy alone and to stimulants alone regarding response (large effect size), without any differences in acceptability (see Table 6).

In head-to-head comparisons, amphetamines outperformed methylphenidate, which outperformed bupropion (large effect sizes) and atomoxetine (small effect size) on the primary efficacy outcome. Amphetamines were superior to atomoxetine in reducing discontinuation due to inefficacy, and better than methylphenidate for aggressive behavior (small effect size), while methylphenidate was superior to atomoxetine regarding acceptability (medium effect size), and to guanfacine regarding less discontinuation due to intolerability (medium effect size). Stimulants were superior to neurofeedback regarding cognition, and neurofeedback outperformed cognitive training on acceptability (see Table 6).

*Autism spectrum disorder*

Results for autism spectrum disorder are shown in Tables 2, 5, 6 and 7.

Aripiprazole was superior to placebo regarding the primary efficacy outcome, as well as response, aggressive behavior, global illness severity, and acceptability (all small effect sizes). Risperidone showed the same profile, yet with a large effect size regarding response. Both aripiprazole and risperidone were not different from placebo concerning discontinuation due to intolerability (see Table 2).

Among psychosocial interventions, social skills training had a small to large effect size regarding the primary efficacy outcome and functioning, and CBT had a large effect concerning anxiety across different control groups. Parent-child interaction therapy and other mixed psychosocial interventions had a small to medium effect size for the primary efficacy outcome vs. TAU, as well as a small effect regarding cognition. Parent-child interaction therapy also improved aggression (medium effect size), irritability (medium effect size), and functioning (large effect size). Finally, behavioral therapy with an imitative component had a large effect size for the primary efficacy outcome against other active psychosocial interventions without the imitative component (see Tables 5, 6 and 7).

*Depressive disorders*

Results for depressive disorders are shown in Tables 3, 5, 6 and 7.

Fluoxetine was the only pharmacological intervention that was superior to placebo on the primary efficacy outcome (medium effect size), as well as on response and remission (both small effect size). Nortriptyline worsened the primary efficacy outcome (large effect size), imipramine increased all-cause drop-out (small effect size), and imipramine, venlafaxine and duloxetine increased discontinuation due to intolerability (small to medium effect size). Venlafaxine increased suicidality (large effect size) (see Table 3).

Among psychosocial interventions, a large effect size on the primary efficacy outcome was apparent for interpersonal therapy, problem-solving therapy, family therapy, and CBT vs. waiting list/no treatment. However, these results were not confirmed vs. placebo or vs. TAU, except for interpersonal therapy, that remained superior when compared to placebo and TAU (medium effect size) (see Table 3).

CBT was also superior to mixed interventions regarding the primary efficacy outcome (medium effect size), and to selective serotonin reuptake inhibitors (SSRIs) regarding suicidality (small effect size) (see Tables 6 and 7). Psychodynamically-oriented psychotherapy had a small effect size advantage regarding response, but no significant effect on the primary efficacy outcome vs. placebo (see Table 3).

As a combination treatment, CBT plus fluoxetine had a medium effect size advantage regarding the primary efficacy outcome vs. placebo, and was also superior concerning remission vs. CBT monotherapy, and functioning vs. antidepressant monotherapy (small effect size) (see Table 6).

*Enuresis*

Results for enuresis are shown in Tables 4 and 6.

Among pharmacological interventions, imipramine outperformed placebo regarding the primary efficacy outcome and response (small effect size), and amitriptyline was superior to placebo with respect to response (small effect size) (see Table 4).

Behavioral therapy with alarm outperformed placebo on the primary efficacy outcome (small effect size) and response (large effect size) vs. waiting list, and maintained a small effect size regarding response vs. placebo (see Table 4).

No clear superior treatment emerged in monotherapy head-to-head comparisons. Combination of desmopressin plus behavioral therapy with alarm was superior to desmopressin alone regarding the primary efficacy outcome (medium effect size) and response (small effect size), while combination of oxybutynin plus imipramine was superior to either imipramine or oxybutynin monotherapy (small effect size) (see Table 6).

*Obsessive-compulsive disorder*

Results for obsessive-compulsive disorder are shown in Tables 4 and 5.

Fluoxetine was the pharmacological intervention with the broadest efficacy, including primary efficacy outcome, response, and global illness severity vs. placebo (small effect sizes). SSRIs as a class also improved response, remission and global illness severity, yet had a higher discontinuation rate due to intolerability than placebo (see Table 4).

As monotherapy psychosocial interventions, CBT and behavioral therapy were superior to waiting list regarding the primary efficacy outcome (medium effect size), response (small effect size), remission (small effect size), quality of life (small effect size), functioning (large effect size), and also against placebo concerning remission (small effect size). Behavioral therapy with exposure response prevention outperformed TAU for both response and acceptability (small effect size) (Table 5).

As a combination treatment, CBT and sertraline outperformed placebo (medium effect size) (see Table 4). No significant differences emerged in head-to-head comparisons.

*Anxiety disorders*

Results for anxiety disorders are shown in Tables 4, 5 and 6.

SSRIs (fluoxetine, fluvoxamine, paroxetine) outperformed placebo regarding the primary efficacy outcome, and response (small to medium effect). Fluoxetine also outperformed placebo with respect to remission (small effect size) (see Table 4). Sertraline reduced suicidality compared with placebo, but paroxetine increased it.

CBT was superior to waiting list in different formats (i.e., individual, Internet, group) regarding the primary efficacy outcome (small to large effect size), depressive symptoms (small effect size), remission (small to large effect size) and quality of life (large effect size). CBT was also superior to placebo with respect to quality of life (large effect size) and to TAU regarding the primary efficacy outcome, remission and functioning (large effect size). Group CBT was superior to individual CBT in head-to-head comparisons (small effect size) (see Table 6).

No meta-analysis compared pharmacological vs. psychosocial interventions or combined treatment strategies.

*Disruptive behavior/dissocial/conduct disorders*

Results for disruptive behavior/dissocial/conduct disorders are shown in Tables 2 and 7.

Among pharmacological interventions, risperidone outperformed placebo across different raters regarding the primary efficacy outcome (medium effect size), aggressive behavior (medium effect size, also in people with intellectual disability), and global illness severity (medium effect size). Aggressive behavior was also improved by lithium and valproate (see Table 2).

Among psychosocial interventions, a combination of parental and child behavioral interventions had a large effect size vs. waiting list concerning the primary efficacy outcome, and a medium effect size vs. a mixed control group (see Tables 2 and 7).

*Eating disorders*

Results for eating disorders are shown in Table 6.

No meta-analysis on pharmacological intervention met the inclusion criteria of this umbrella review. Among psychosocial interventions, family therapy outperformed other interventions in anorexia nervosa regarding the primary efficacy outcome (body weight, small effect size).

*Schizophrenia spectrum disorders*

Results for schizophrenia spectrum disorders are shown in Tables 3 and 6.

For schizophrenia, only pharmacological interventions were covered. All investigated antipsychotics but ziprasidone outperformed placebo, with a small effect size, except for olanzapine and risperidone, which had a large effect size. Small effect sizes emerged regarding response (except for asenapine), and all antipsychotics improved global illness severity. Acceptability was superior vs. placebo for paliperidone, risperidone and olanzapine, without differences for the other antipsychotics. Paliperidone and olanzapine were associated with more discontinuation due to intolerability than placebo, while discontinuation due to inefficacy favored paliperidone, olanzapine, risperidone and ziprasidone (see Table 3).

In head-to-head comparisons, risperidone and second-generation antipsychotics outperformed first-generation antipsychotics (large effect size), and clozapine outperformed olanzapine on the primary efficacy outcome (large effect size) (see Table 6).

*Bipolar disorder*

Results for bipolar disorder are shown in Tables 3 and 6.

Regarding bipolar depression, quetiapine was not superior to placebo regarding the primary efficacy outcome, separating only on global illness severity (small effect size). Regarding mania, aripiprazole was more effective than placebo regarding the primary efficacy outcome (large effect size) and response (small effect size), without differences vs. placebo regarding acceptability, while being superior regarding less discontinuations for inefficacy (see Table 3).

*Other disorders*

Results for tic disorder are shown in Tables 2 and 6. Desipramine and methylphenidate were similar to placebo, but topiramate was superior to haloperidol regarding the primary outcome.

Results for Tourette’s syndrome are shown in Tables 2 and 7. Antipsychotics (including haloperidol, pimozide, risperidone and ziprasidone) and guanfacine were superior to placebo regarding the primary efficacy outcome (both moderate effect size). No significant difference vs. placebo emerged for methylphenidate (see Table 2).Among psychosocial interventions, behavioral therapy outperformed waiting list or low intensity psychosocial intervention (medium effect size) regarding the primary efficacy outcome (see Table 7).

Results for encopresis are shown in Table 5. No pharmacological intervention was eligible. Behavioral therapy outperformed TAU regarding the primary efficacy outcome and response (small effect size).

Results for developmental coordination disorders are shown in Table 2. In the single meta-analysis meeting inclusion criteria, skills training had no significant effect vs. waiting list on motor coordination.

Results for PTSD are shown in Table 4. No pharmacological intervention met inclusion criteria. CBT was superior regarding the primary efficacy outcome, response and depressive symptoms vs. waiting list (large effect sizes).

DISCUSSION

Pooling top-tier evidence from altogether 104 MAs/NMAs of RCTs reporting on the effects of pharmacological, psychosocial, and brain stimulation interventions targeting 20 different outcomes in 15 mental disorders or groups of mental disorders, this umbrella review provides a comprehensive meta-analytic view of the evidence base regarding the efficacy, acceptability and other relevant outcomes of psychiatric treatments in children and adolescents.

Considered together with a complementary umbrella review published in this journal14, focusing on the detailed evaluation of tolerability and safety of pharmacological interventions, the current review can inform clinicians, youth and their families, as well as other stakeholders, in making evidence-based decisions regarding the choice and use of pharmacological, psychosocial and brain stimulation interventions in children/adolescents, in monotherapy and in combination. On the basis of these reviews, some evidence-based recommendation can be made.

For ADHD, amphetamines and methylphenidate are the most effective interventions on a broad set of outcomes. Whilst amphetamines outperform methylphenidate on the primary efficacy outcome, methylphenidate is the medication least different from placebo concerning safety14. Some evidence is available regarding behavioral therapy, covering a narrow set of efficacy outcomes, and with small effect sizes compared with those for medications. Importantly, whilst social skills training shows promising results against waiting list, no evidence is available comparing this intervention with placebo. Hence, amphetamines or methylphenidate can be considered the first-line treatment, augmented with alpha-2 agonists if needed, and ideally in combination with behavioral therapy as an optimal treatment regimen. Behavioral therapy could be considered if medications are contraindicated.

For autism, aripiprazole and risperidone are the pharmacological treatment options of choice. However, various psychosocial interventions have proven efficacy on a broad set of outcomes, ranging from anxiety (CBT), to irritability, aggressive behavior and functioning (PCIT), to the primary efficacy outcome and functioning (SST, and BT with imitative component). These benefits are not only observed vs. waiting list, but also against other active interventions. Given the different outcomes that these treatment modalities target, a variety of therapeutic tools can be considered, according to the patient’s and family’s resources, needs and choice, as well as the disease course and the presence of environmental stressors.

For depressive disorders in youth, fluoxetine is the only evidence-based pharmacological option. All other medications do not improve depression vs. placebo, but placebo effects are considerable. Imipramine, nortriptyline, and likely also venlafaxine should be avoided, given poor acceptability, tolerability and safety. As an alternative to medications, IPT and CBT should be considered the only psychosocial interventions outperforming placebo or other active interventions. The optimal treatment regimen is the combination of CBT with fluoxetine, which is superior to either monotherapy.

For enuresis, imipramine is the most effective pharmacological intervention. It can be combined with oxybutynin to maximize efficacy. However, due to the potential problems with tolerability of this medication in youth, psychosocial interventions should be tried first, including especially alarm BT, that is supported by the largest body of evidence. No difference emerges among different types of alarms, and alarm maintains its efficacy after stopping the intervention86.

For obsessive-compulsive disorder, fluoxetine and SSRIs as a class should be considered the first-line pharmacological treatment. Among psychosocial interventions, CBT and BT with exposure response prevention are effective options. No meta-analytic evidence supports the combination of pharmacological and psychosocial interventions; hence, if fluoxetine/SSRIs are ineffective, a switch to psychosocial interventions should be performed, and viceversa71.

For anxiety disorders, fluoxetine, and fluvoxamine are evidence-based pharmacological treatment strategies. Among psychosocial interventions, CBT – and in particular group CBT – should be offered as first-line treatment, likely before medications, given the large effect size and broad beneficial effect even vs. placebo in children and adolescents.

For disruptive behavior/dissocial/conduct disorders, risperidone emerges as the most effective pharmacological agent, but different types of behavioral treatment (including parent training) should be regarded as the first-line treatment options118,119.

For anorexia nervosa in children and adolescents, family therapy is the intervention supported by the most significant evidence.

For schizophrenia spectrum disorders, antipsychotic treatment is the cornerstone of treatment. All tested antipsychotics, except for ziprasidone, have broadly similar superior efficacy vs. placebo, with olanzapine and risperidone being the most effective, and lurasidone/aripiprazole being also effective and a more tolerable treatment option102. Ideally, starting with safer medications minimizing the risk of adverse events and maximizing adherence is a recommended strategy14.

For bipolar disorder, little meta-analytic evidence is available overall. For mania, the only positive data are available for aripiprazole, yet lithium is also an evidence-based treatment based on RCT evidence120. For bipolar depression, only quetiapine is superior to placebo, and only on a single outcome, namely global illness severity, but not on the primary symptom outcome. This finding is different from adults121, and at least partially due to the larger placebo effects in youth. Our umbrella review did not include lurasidone and olanzapine/fluoxetine combination, as no meta-analysis has been conducted on them, but these are evidence-based options to treat bipolar depression in youth based on single RCTs122,123, which led to their approval by the US Food and Drug Administration for bipolar depression in children and adolescents.

The available evidence presented in this umbrella review is not equally large across individual disorders, and also across monotherapies with pharmacological or psychosocial interventions. Even less meta-analytic data are available for head-to-head studies, within and across treatment modalities, and regarding combination treatments. Furthermore, little meta-analytic evidence exists on treatment-resistant youth with a given mental disorder. This is concerning, as early illness onset and disruption of healthy development may portend poorer response and outcomes, requiring information on non-responding conditions after first- and second-line treatments have been tried.

It is also of concern that, among the 104 included meta-analyses, virtually no meta-analysis reported data on long-term treatment or relapse prevention. This is problematic, as most of these disorders are chronic and require long-term treatment.

This umbrella review clearly shows that large effect sizes emerge for psychosocial interventions that are compared with waiting list or no treatment, where no placebo or expectation of study effect diminishes the treatment effect size. However, when those treatments are compared against psychological placebo or minimally active comparisons, significant effects either diminish in magnitude or disappear. This finding is relevant for indirect comparisons with pharmacological trials, in which the use of placebo makes the effect size appear smaller. The much greater difficulty of blinding treatment assignment in psychosocial trials is also to be taken into account. The risk of inflated effect sizes due to weak and methodologically flawed comparators (e.g., waiting list, no intervention), as shown for instance in the case of CBT in pediatric OCD121, is that such interventions might be preferred to other superior treatments, delaying response and remission.

The results from this umbrella review should be considered within its limitations. First, we only considered evidence that was evaluated quantitatively via MAs/NMAs. This approach has excluded data from RCTs that have not (yet) been meta-analyzed. In particular, Internet-based psychosocial interventions, whose development has been recent and which may be particularly favored by youth125,126, have not been sufficiently covered.

Second, we focused mainly on efficacy outcomes, while choices need to be made considering both efficacy and tolerability/safety. However, we included all-cause discontinuation as a global acceptability measure, as well as discontinuation due to intolerability as a core tolerability outcome, because these two events are typically measured and reported across both pharmacological and non-pharmacological treatment modalities. Detailed tolerability outcomes of pharmacological interventions in youth with mental disorders, that can be used to complement the present work on efficacy, have been recently published in this journal14. Such detailed data are not generally reported for psychosocial interventions, which is currently a major unmet need127.

Third, as mentioned above, most meta-analytic evidence concerns the acute and short-term treatment effects, and much more data are required regarding the efficacy and safety of long-term and relapse prevention interventions for mental disorders in youth. Fourth, most evidence is available for monotherapy and vs. placebo/no treatment, although combination and augmentation treatments across and within pharmacological and psychosocial treatment modalities are commonly used in clinical practice, in youth as well as in adults128. Fifth, although 14 of the 104 included meta-analyses were NMAs that allow for direct and indirect head-to-head comparisons, most data were not derived from direct comparisons of active treatments, limiting the confidence with which comparative treatment choices can be made.

Sixth, since design, population and illness characteristics, as well as choice of control groups and blinding methods influence effect sizes, and these characteristics often differ substantially between pharmacological and non-pharmacological trials, indirect comparisons of effect sizes across these treatment modalities need to be interpreted with caution. To overcome this limitation, more head-to-head comparisons and combination trials need to be conducted both within and across treatment modalities. Finally, we focused on those disorders that are most common and studied in youth, maximizing the chance of finding meta-analytic evidence, but other mental conditions could also be of interest.

Despite these limitations, inherent in the umbrella review methodology and available RCT data, this study provides the most comprehensive account of the available RCT evidence of pharmacological, psychosocial and brain stimulation interventions for the main psychiatric disorders in childhood and adolescents. The large body of literature reviewed here can inform future research aimed at addressing identified gaps, as well as current clinical care and guidelines regarding the choice of interventions for mental health conditions in youth, merging state-of-the-art efficacy and acceptability data with information on tolerability and safety.

Supplementary materials

Supplementary materials associated with this article can be accessed in: <https://osf.io/2awu4/>

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Conflict of interest

CUC has been a consultant and/or advisor to or has received honoraria from: Acadia, Alkermes, Allergan, Angelini, Axsome, Gedeon Richter, Gerson Lehrman Group, Indivior, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Rovi, Supernus, and Teva. He has received grant support from Bendheim Foundation, Berlin Institute of Health, Janssen, National Institute of Mental Health, USA, Patient Centered Outcomes Research Institute, and Takeda. He is also a stock option holder of LB Pharma.

MS has received honoraria/served in advisory board for Angelini, Lundbeck.

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All other authors declare no relevant conflict of interest.

Authors’ contribution

CUC, MS drafted the protocol, which was then reviewed and approved by all authors. All authors conducted literature screening, data extraction. MS, AE, GC run analyses. AE, CUC, MS, SC drafted the first version of the manuscript. All authors critically reviewed, contributed to, and finally approved the manuscript.

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Records identified through database searching  
(N=5,137)

Additional records identified through other sources  
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Records after duplicates removed  
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Records excluded  
(N=4,321)

Records screened  
(N=5,231)

Full-text articles excluded  
(N=806)

Full-text articles assessed for eligibility  
(N=910)

Full-text articles included (N=104)

MA: 90

NMA: 14

Figure 1 PRISMA flow chart

Table 1 Network and pairwise meta-analyses of randomized controlled trials (RCTs) of pharmacological, psychosocial and brain stimulation interventions in children and adolescents with mental disorders included in the umbrella review

|  | Source | Number of RCTs/ patients | Intervention | Controls | Outcomes | A | C |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Anxiety disorders | | | | | | | |
| Wang et al79 | MA | 115/7,719 | AD | PBO | PE, REM | 10 | 4 |
| Dobson et al11 | NMA | 22/2,623 | AD | PBO | RES, ACD, AED, S | 7 | 5 |
| Zhang et al80 | MA | 7/358 | CB | WL/NT | PE | 9 | 2 |
| James et al12 | MA | 87/5,964 | CB | PBO, WL/NT, TAU, PS | PE, REM, DEP, F, ACD | 11 | 3 |
| Zhou et al78 | NMA | 101/6,625 | CB | PBO, WL/NT, TAU, PS | PE, QoL, ACD | 11 | 2 |
| Sigurvinsdóttir et al81 | MA | 81/5,913 | CB | WL/NT, TAU, PS | REM | 10 | 1 |
| James82 | MA | 41/1,955 | CB | TAU, PS | PE, REM | 11 | 1.5 |
| Anorexia nervosa | | | | | | | |
| Fisher et al99 | MA | 21/1,407 | FB | TAU, PS | PE, ACD, REM | 10 | 1 |
| van den Berg et al100 | MA | 15/1,279 | PS | TAU | PE | 9 | 2 |
| Zeeck et al 97 | NMA | 18/1,247 | FB, PSD-O | PS | PE | 7 | 1 |
| Social anxiety disorder | | | | | | | |
| Yang et al83 | MA | 17/1,134 | CB | PBO, WL/NT | PE, REM, DEP, QoL, ACD | 10 | 2 |
| Kreuze et al84 | MA | 42/3,239 | CB | PBO, TAU, LIP | AG, F | 10 | 2.5 |
| Attention-deficit/hyperactivity disorder (ADHD) | | | | | | | |
| Cortese et al5 | NMA | 133/18,199 | AD, STIM, α2 | PBO, AD, STIM | PE, AED, GLO | 11 | 9 |
| Otasowie et al22 | MA | 6/216 | AD | PBO | PE, GLO | 10 | 3 |
| Punja et al 23 | MA | 23/2,675 | STIM | PBO | PE, COG, GLO | 10 | 4 |
| Stuhec et al34 | MA | 28/4,699 | AD | PBO | PE | 8 | 2 |
| Luan et al21 | NMA | 73/15,025 | AD, STIM, α2 | PBO, PHARMA | PE, AED, ID | 7 | 4 |
| Catalá-López et al20 | NMA | 190/26,114 | AP, AD, STIM, α2, CB, CT, NF, COMB | PBO | RES, ACD, GLO | 10 | 4 |
| Schachter et al36 | MA | 62/2,897 | STIM | PBO | AG | 9 | 1 |
| Schwartz et al37 | MA | 25/3,928 | AD, STIM | PBO | AG, F, QoL, S | 7 | 5 |
| Coghill et al38 | MA | 60/1,993 | STIM | PBO | COG | 8 | 2 |
| Storebø et al39 | MA | 185/12,245 | STIM | PBO | QoL | 8 | 5 |
| Bangs et al40 | MA | 32/7,248 | AD, STIM | PBO | S | 3 | 4 |
| Hirota et al41 | MA | 12/2,276 | α2+ | PBO | PE, ACD, AED, ID | 6 | 3.5 |
| Storebø et al42 | MA | 25/2,690 | SKILL, COMB | WL/NT | PE, COG, F | 11 | 2 |
| Sun et al24 | MA | 8/423 | STIM | PBO | PE, ACD, AED | 11 | 2 |
| Battagliese et al25 | MA | 24/1,690 | BT | MIX | PE, AG, COG, F | 7 | 1 |
| Faraone et al26 | MA | 4/216 | STIM | STIM | AG | 2 | 3 |
| Van Doren et al27 | MA | 10/506 | NF | PHARMA, PS | PE, RES, ACD | 8 | 2 |
| Cortese et al28 | MA | 16/759 | CT | MIX | PE, COG | 11 | 1 |
| Daley et al29 | MA | 32/2,077 | BT | MIX | PE, COG | 9 | 2 |
| Bikic et al30 | MA | 12/1,054 | SKILL | MIX | PE, COG | 8 | 2 |
| Mulqueen et al31 | MA | 8/399 | BT | MIX | PE | 6 | 1 |
| Cortese et al32 | MA | 13/520 | NF | MIX | PE, COG | 9 | 1.5 |
| Bussalb et al33 | MA | 16/706 | NF | MIX | PE | 4 | 2 |
| Faraone et al35 | MA | 7/384 | STIM | PBO | AG | 2 | 2 |
| Autism spectrum disorder | | | | | | | |
| Maneeton et al44 | MA | 3/408 | AP | PBO | PE, RES, GLO | 7 | 4 |
| Maneeton et al52 | MA | 7/372 | AP | PBO | REL, RES | 7 | 3.5 |
| Zhou et al53 | MA | 64/3,499 | STIM | PBO | PP | 9 | 3 |
| Murza et al54 | MA | 16/837 | ST | WL/NT | F | 8 | 0.5 |
| Fletcher-Watson et al56 | MA | 22/695 | ST | WL/NT, TAU | F | 10 | 1 |
| Sturman et al55 | MA | 4/113 | STIM | PBO | PE | 10 | 1 |
| Cohen et al57 | MA | 15/995 | AP | PBO | RES | 5 | 1 |
| Hirota et al58 | MA | 7/171 | MS | PBO | RES, AG, ACD, AED, ID | 6 | 4 |
| Fallah et al43 | NMA | 8/878 | AP | PBO, AP | AG | 7 | 1 |
| D’Alò et al59 | MA | 15/1,124 | AP | PBO | ACD, AED | 9 | 5 |
| Ospina et al60 | MA | 69/2,585 | BT | WL/NT, PS | PE | 9 | 1 |
| Reichow et al61 | MA | 5/196 | SKILL | WL/NT | PE | 10 | 1 |
| James et al12 | MA | 87/5,964 | CB | WL/NT, TAU | ANX | 11 | 0.5 |
| Tachibana et al 62 | MA | 32/594 | PS | TAU | PE | 11 | 1 |
| Nevill et al63 | MA | 19/1,205 | PCI | TAU/LIP, MIX | PE, COG | 5 | 1 |
| Yu et al45 | MA | 14/555 | BT | TAU | PE, F | 9 | 0 |
| Oono et al46 | MA | 17/919 | PCI | MIX | PE, F, GLO | 10 | 1 |
| Parsons et al47 | MA | 21/925 | SKILL | MIX | PE | 9 | 1 |
| Kreslins et al48 | MA | 10/470 | CB | MIX | ANX | 9 | 0 |
| Tarver et al49 | MA | 9/521 | PCI | MIX | AG | 8 | 2 |
| Soares et al50 | MA | 18/1,266 | SKILL | MIX | F | 8 | 2 |
| Postorino et al51 | MA | 8/653 | PCI | MIX | IR | 8 | 1 |
| Bipolar disorder, depressive episode | | | | | | | |
| Maneeton et al106 | MA | 3/251 | AP | PBO | PE, RES, REM, GLO, ACD, AED | 9 | 3 |
| Bipolar, manic episode | | | | | | | |
| Meduri et al107 | MA | 22/5,437 | AP | PBO | PE, RES, ACD, AED, ID | 10 | 5 |
| Liu et al108 | MA | 46/2,666 | MS | PBO | RES | 7 | 6 |
| Jochim et al109 | MA | 25/3,252 | MS, AP | PBO, MS | ACD | 10 | 4 |
| Bulimia nervosa | | | | | | | |
| Linardon et al101 | MA | 79/NR | CB | PS | PE | 6 | 0 |
| Depressive disorders | | | | | | | |
| Zhou et al10 | NMA | 71/9,510 | AD, PSD-O, FB, CB, COMB | PBO, WL/NT, TAU/LIP, PHARMA, PS | PE, ACD, S | 11 | 5 |
| Cipriani et al7 | NMA | 34/5,260 | AD | PBO, PHARMA | RES, AED | 11 | 5 |
| Spielmans & Gerwig64 | MA | 8/1,756 | AD | PBO | QoL | 5 | 5 |
| Kato et al65 | MA | 40/8,890 | AD | PBO | REL | 9 | 3 |
| Whittington et al66 | MA | 2/376 | AD | PBO | REM | 9 | 2.5 |
| Watanabe et al67 | MA | 27/1,744 | PSD-O | WL/PBO | RES | 7 | 2 |
| Cox et al68 | MA | 9/882 | AD, CB, COMB | PHARMA, PS | REM, S | 10 | 3 |
| Dubicka et al69 | MA | 5/1,206 | COMB | PHARMA, PS | RES, F, S | 7 | 3 |
| Klein et al70 | MA | 11/809 | CB | MIX | PE | 8 | 4 |
| Disruptive behavior/dissocial/conduct disorders | | | | | | | |
| Seida et al92 | MA | 62/NR | AP | PBO | PE, AG, GLO | 9 | 3.5 |
| Loy et al93 | MA | 10/896 | AP | PBO | PE, AG | 10 | 4 |
| Pringsheim et al94 | MA | 18/1,195 | MS | PBO | AG | 10 | 2 |
| Ipser & Stein95 | MA | 14/823 | PHARMA | PBO | AG, ACD, GLO, RES | 6 | 1.5 |
| Battagliese et al25 | MA | 24/1,690 | CB | WL/NT, MIX | PE | 7 | 1.5 |
| McQuire et al96 | MA | 14/912 | AP, MS | PBO | AG | 8 | 2 |
| Developmental coordination disorder | | | | | | | |
| Miyahara et al116 | MA | 15/649 | SKILL | WL/NT | PE | 10 | 1 |
| Eating disorders | | | | | | | |
| Couturier et al98 | MA | 6/369 | FB | PS | REM | 8 | 3 |
| Encopresis | | | | | | | |
| Freeman et al114 | MA | 10/562 | COMB | TAU | PE, RES | 7 | 1 |
| Brazzelli et al115 | MA | 21/1,371 | COMB | TAU | RES | 10 | 1 |
| Enuresis | | | | | | | |
| Caldwell et al86 | MA | 74/5,983 | BT, COMB | PHARMA, PS, WL/NT | PE, RES | 11 | 1 |
| Caldwell et al87 | MA | 64/4,071 | AD, COMB | PBO, PHARMA, PS | PE, RES | 11 | 1 |
| Caldwell et al88 | MA | 16/1,643 | BT | PS, WL/NT | RES | 10 | 1 |
| Buckley et al89 | MA | 27/1,803 | SKILL, COMB | TAU, PHARMA | REM | 10 | 1 |
| Deshpande et al90 | MA | 40/2,440 | AD, COMB | PHARMA | RES, REL | 10 | 1 |
| Peng et al91 | MA | 15/1,502 | PHARMA | PS | ACD | 9 | 4 |
| Song et al85 | NMA | 18/1,649 | PHARMA, COMB | PHARMA, PS | RES, REL | 9 | 4 |
| Obsessive-compulsive disorder | | | | | | | |
| Skapinakis et al71 | NMA | 86/15,585 | AD, CB, COMB | PBO, WL/NT, PHARMA, PS | PE, ACD | 10 | 3 |
| Maneeton et al72 | MA | 3/188 | AD | PBO | RES, GLO | 9 | 2 |
| McGuire et al73 | MA | 20/1,296 | AD, CB | PBO, TAU/LIP, WL/NT | RES, REM | 8 | 1 |
| Locher et al74 | MA | 36/6,778 | AD | PBO | AED | 10 | 4 |
| Geller75 | MA | 12/1,044 | AD | PBO | GLO | 8 | 3 |
| Uhre et al 76 | MA | 12/791 | CB, AD | PBO, WL/NT, PS | REM, F, QoL | 9 | 1 |
| Johnco et al 77 | MA | 21/1,423 | CB, AD | PBO, WL/NT, TAU/LIP, PS | ACD | 6 | 1 |
| Post-traumatic stress disorder | | | | | | | |
| Gillies et al117 | MA | 14/758 | CB | WL/NT, TAU/LIP | PE, RES, ANX, DEP, ACD | 10 | 1 |
| Schizophrenia spectrum disorders | | | | | | | |
| Krause et al102 | NMA | 28/3,003 | AP | PBO, PHARMA | PE, RES, ACD, ID | 11 | 3 |
| Arango et al 103 | NMA | 13/2,210 | AP | PBO, PHARMA | GLO, AED | 9 | 7 |
| Pagsberg et al8 | NMA | 12/2,158 | AP | PBO, PHARMA | GLO | 8 | 3 |
| Sarkar & Grover104 | MA | 15/995 | AP | PHARMA | PE | 5 | 1 |
| Kumar et al105 | MA | 13/1,112 | AP | PHARMA | AED | 8 | 1 |
| Tic disorder | | | | | | | |
| Bloch et al110 | MA | 9/477 | STIM, AD | PBO | PE | 4 | 1 |
| Yu et al111 | MA | 15/1,070 | MS | PHARMA | RES | 7 | 3 |
| Tourette’s syndrome | | | | | | | |
| Hollis et al112 | MA | 40/2,422 | AP, α2, STIM, BT | PBO, MIX | PE | 8 | 1 |
| Zheng et al113 | MA | 6/528 | AP | PHARMA | PE | 10 | 2 |

MA – meta-analysis, NMA – network meta-analysis, A – AMSTAR, C – AMSTAR-Content (median), AD – antidepressants, CB – cognitive-based, FB – family-based, PS – active psychosocial, PSD-O – psychodynamic-oriented, STIM – stimulants, α2 – α2-agonists (+=augmentation with), AP – antipsychotics, CT – cognition-targeted, NF – neurofeedback, COMB – combination of more than one treatment, SKILL – skills training, BT – behavioral treatment, MS – mood stabilizers, PCI – parent-child interaction, PHARMA – mixed medications, PBO – placebo, WL – waiting list, NT – no treatment, TAU – treatment as usual, LIP – low-intensity psychosocial intervention, MIX – mixed active/inactive control group, PE – primary efficacy outcome, REM – remission, REL – relapse, RES – response, S – suicidality, ACD – all-cause discontinuation, AED – discontinuation due to adverse events, ID – discontinuation due to inefficacy, DEP – depressive symptoms, ANX – anxiety symptoms, AG – aggressivity, QoL – quality of life, GLO – global illness severity, COG – cognition, F – functioning, NR – not reported

Table 2 Efficacy and effectiveness of pharmacological, psychosocial and brain stimulation interventions vs. inactive control in children/adolescents with neurodevelopmental and disruptive behavior/dissocial/conduct disorders

| Outcome | Intervention | Effect size (95% CI) | Control | Number of RCTs/patients | Q |
| --- | --- | --- | --- | --- | --- |
| Attention-deficit/hyperactivity disorder (ADHD) | | | | | |
| *Pharmacological interventions* | | | | | |
| Efficacy (clinician-rated) | Amphetamines  Methylphenidate  Clonidine  Guanfacine  Modafinil  Atomoxetine | SMD=–1.02 (–1.19 to –0.85)  SMD=–0.78 (–0.93 to –0.62)  SMD=–0.71 (–1.17 to –0.24)  SMD=–0.67 (–0.85 to –0.50)  SMD=–0.62 (–0.84 to –0.41)  SMD=–0.56 (–0.66 to –0.45) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 46/9,926  46/9,926  46/9,926  46/9,926  46/9,926  46/9,926 | H  H  H  H  H  H |
| Efficacy (teacher-rated) | Desipramine  Methylphenidate  Modafinil  Amphetamines  Guanfacine  Atomoxetine | SMD=–0.97 (–1.66 to –0.28)  SMD=–0.82 (–1.16 to –0.48)  SMD=–0.76 (–1.15 to –0.37)  SMD=–0.55 (–0.83 to –0.27)  SMD=–0.63 (–1.62 to 0.35)  SMD=–0.32 (–0.82 to 0.18) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 2/89  16/1,843  16/1,843  5/745  16/1,843  16/1,843 | L  H  H  M  H  H |
| Efficacy (parent-rated) | Desipramine  Amphetamines  Methylphenidate  Atomoxetine  Modafinil  Bupropion  Guanfacine | SMD=–1.42 (–1.99 to –0.85)  SMD=–1.07 (–1.36 to –0.79)  SMD=–0.84 (–0.95 to –0.72)  SMD=–0.60 (–0.71 to –0.50)  SMD=–0.46 (–0.61 to –0.31)  SMD=–0.32 (–0.69 to 0.05)  SMD=–0.23 (–0.90 to 0.45) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 2/99  23/3,796  23/3,796  23/3,796  23/3,796  2/124  23/3,796 | L  H  H  H  H  L  H |
| Efficacy (mixed-rated) | Atomoxetine  Amphetamines  Methylphenidate  Guanfacine  Clonidine | SMD=–0.17 (–0.23 to –0.11)  SMD=–0.18 (–0.28 to –0.09)  SMD=–0.14 (–0.21 to –0.08)  SMD=–0.16 (–0.26 to –0.05)  SMD=–0.10 (–0.23 to 0.03) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 36/7,579  36/7,579  36/7,579  36/7,579  36/7,579 | M  M  M  M  M |
| Response | Desipramine Amphetamines  Modafinil  Methylphenidate  Clonidine  Atomoxetine  Guanfacine | OR=36.76 (9.17-214)  OR=7.45 (5.1-11.09)  OR=5.51 (3.04-10.32)  OR=5.26 (4.09-6.82)  OR=3.96 (1.89-8.41)  OR=3.63 (2.81-4.73)  OR=3.29 (2.27-4.82) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 113/19,398  113/19,398  113/19,398  113/19,398  113/19,398  113/19,398  113/19,398 | M  M  M  M  M  M  M |
| Aggressive behavior | Amphetamines  Methylphenidate  Atomoxetine | SMD=–1.15 (–1.38 to –0.93)  SMD=–0.26 (–1.10 to 0.68)  RR=1.34 (0.91 to 1.97) | PBO/Sham  PBO/Sham  PBO/Sham | 3/84  2/181  15/2,067 | L  L  M |
| Cognition: executive memory | Methylphenidate | SMD=–0.26 (–0.39 to –0.13) | PBO/Sham | 7/468 | L |
| Cognition: non-executive memory | Methylphenidate | SMD=–0.60 (–0.79 to –0.41) | PBO/Sham | 8/635 | L |
| Cognition: reaction time | Methylphenidate | SMD=–0.21 (–0.30 to –0.12) | PBO/Sham | 21/1,095 | L |
| Cognition: response inhibition | Methylphenidate | SMD=–0.41 (–0.55 to –0.27) | PBO/Sham | 16/846 | L |
| Acceptability | Clonidine  Methylphenidate  Aripiprazole  Modafinil  Desipramine  Amphetamines  Guanfacine  Atomoxetine  Bupropion | OR=0.40 (0.20-0.78)  OR=0.59 (0.46-0.75)  OR=0.61 (0.02-25.34)  OR=0.67 (0.37-1.24)  OR=0.70 (0.17-2.89)  OR=0.78 (0.52-1.18)  OR=0.79 (0.54-1.14)  OR=0.85 (0.68-1.07)  OR=1.54 (0.39-6.76) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 171/22,961  171/22,961  171/22,961  171/22,961  171/22,961  171/22,961  171/22,961  171/22,961  171/22,961 | M  M  M  M  M  M  M  M  M |
| Tolerability | Methylphenidate  Modafinil  Amphetamines  Clonidine  Bupropion  Atomoxetine  Guanfacine | OR=1.31 (0.79-2.25)  OR=1.34 (0.57-3.18)  OR=1.38 (0.64-3.00)  OR=2.32 (0.63-8.94)  OR=3.60 (0.34-130)  OR=1.48 (1.01-2.18)  OR=3.39 (1.93-6.3) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 60/12,188  60/12,188  60/12,188  58/NR  60/12,188  60/12,188  60/12,188 | M  M  M  H  M  M  M |
| Discontinuation due to inefficacy | Amphetamine  Clonidine  Methylphenidate  Guanfacine  Atomoxetine  Bupropion | OR=0.11 (0.05-0.20)  OR=0.29 (0.13-0.56)  OR=0.31 (0.18-0.53)  OR=0.37 (0.26-0.54)  OR=0.47 (0.33-0.67)  OR=1.97 (0.19-57.4) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 45/9,087  45/9,087  45/9,087  45/9,087  45/9,087  45/9,087 | M  M  M  M  M  M |
| Functioning | Atomoxetine | SMD=–0.48 (–0.62 to –0.33) | PBO/Sham | 8/1,308 | M |
| Functioning: academic | Amphetamines | SMD=–0.56 (–0.73 to –0.39) | PBO/Sham | 8/826 | M |
| Global illness improvement | Amphetamines  Atomoxetine  Guanfacine  Methylphenidate  Modafinil  Clonidine | OR=7.71 (5.52-10.77)  OR=2.28 (1.38-3.76)  OR=3.63 (2.36-5.57)  OR=5.57 (3.99-7.79)  OR=3.22 (1.91-5.43)  OR=2.78 (0.91-8.53) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 40/NR  40/NR  40/NR  40/NR  40/NR  40/NR | H  H  H  H  H  H |
| Global illness severity | Amphetamines  Desipramine | SMD=–0.86 (–1.72 to –0.01)  OR=26.41 (7.41-94.18) | PBO/Sham  PBO/Sham | 2/86  2/103 | M  L |
| Quality of life | Methylphenidate  Atomoxetine | SMD=–0.61 (–0.80 to –0.42)  SMD=–0.39 (–0.50 to –0.28) | PBO/Sham  PBO/Sham | 3/514  16/2,361 | M  M |
| Suicide attempt | Atomoxetine | RR=0.84 (0.03-20.00) | PBO/Sham | 23/3,883 | L |
| Suicidal ideation | Atomoxetine | RR=1.67 (0.83-3.36) | PBO/Sham | 15/2,517 | M |
| *Pharmacological augmentation* | | | | | |
| Efficacy | α2-agonists + stimulants | SMD=–0.36 (–0.51 to –0.21) | PBO/Sham | 3/719 | M |
| Acceptability | α2-agonists + stimulants | RR=0.74 (0.37-1.48) | PBO/Sham | 3/726 | L |
| Tolerability | α2-agonists + stimulants | RR=0.77 (0.05-12.50) | PBO/Sham | 3/726 | L |
| Discontinuation due to inefficacy | α2-agonists + stimulants | RR=0.49 (0.21-1.13) | PBO/Sham | 3/726 | M |
| *Psychosocial interventions* | | | | | |
| Efficacy (mixed-rated) | Social skills training | SMD=–0.39 (–0.63 to –0.15) | WL/NT | 15/2,857 | L |
| Efficacy (teacher-rated) | Social skills training | SMD=–0.26 (–0.47 to –0.05) | WL/NT | 14/1,379 | M |
| Efficacy (parent-rated) | Social skills training | SMD=–0.54 (–0.81 to –0.26) | WL/NT | 11/1,206 | L |
| Efficacy (clinician-rated) | Social skills training | SMD=–3.15 (–9.88 to 3.57) | WL/NT | 2/107 | L |
| Response | Behavioral therapy  Cognitive training | OR=2.97 (1.53-5.88)  OR=0.70 (0.12-3.87) | PBO/Sham  PBO/Sham | 113/19,398  113/19,398 | M  M |
| Acceptability | Behavioral therapy  Cognitive training | OR=0.58 (0.33-0.99)  OR=1.32 (0.71-2.52) | PBO/Sham  PBO/Sham | 171/22,961  171/22,961 | M  M |
| Functioning: academic | Social skills training | SMD=–0.15 (–0.31 to 0.01) | WL/NT | 5/642 | M |
| Global illness severity | Behavioral therapy  Cognitive training | OR=2.99 (1.21-7.31)  OR=0.39 (0.01-5.80) | PBO/Sham  PBO/Sham | 113/19,398  113/19,398 | M  M |
| Functioning: social skills (mixed-rated) | Social skills training | SMD=–0.29 (–0.47 to –0.11) | WL/NT | 19/2,649 | L |
| Functioning: social skills (parent-rated) | Social skills training + parental involvement  Social skills training | SMD=–0.43 (–0.70 to –0.15)  SMD=–0.19 (–0.32 to –0.06) | WL/NT  WL/NT | 4/337  15/1,609 | L  M |
| Functioning: social skills (teacher-rated) | Social skills training + parental involvement  Social skills training | SMD=–0.15 (–0.41 to 0.12)  SMD=–0.11 (–0.22 to 0.00) | WL/NT  WL/NT | 4/632  11/1,271 | M  M |
| Functioning: emotional (mixed-rated) | Social skills training | SMD=0.20 (–0.01 to 0.41) | WL/NT | 5/353 | L |
| Functioning: emotional (parent-rated) | Social skills training | SMD=0.27 (–0.05 to 0.59) | WL/NT | 3/173 | L |
| Functioning: emotional (teacher-rated) | Social skills training | SMD=0.02 (–0.68 to 0.72) | WL/NT | 2/129 | L |
| *Brain stimulation interventions* | | | | | |
| Response | Neurofeedback | OR=1.96 (0.52-8.26) | PBO/Sham | 113/19,398 | M |
| Acceptability | Neurofeedback | OR=0.59 (0.31-1.14) | PBO/Sham | 171/22,961 | M |
| *Combined interventions* | | | | | |
| Response | Methylphenidate + parent training  Methylphenidate + clonidine  Atomoxetine + parent training | OR=55.63 (3.18-29.52x102)  OR=21.91 (5.52-105.40)  OR=2.48 (0.51-11.79) | PBO/Sham  PBO/Sham  PBO/Sham | 113/19,398  113/19,398  113/19,398 | M  M  M |
| Acceptability | Methylphenidate + clonidine | OR=0.32 (0.13-0.77) | PBO/Sham | 171/22,961 | M |
| ADHD and disorders of intellectual development | | | | | |
| Efficacy | Methylphenidate | SMD=–0.88 (–1.14 to –0.61) | PBO/Sham | 8/424 | L |
| Acceptability | Methylphenidate | OR=1.68 (0.68-4.14) | PBO/Sham | 4/215 | L |
| Tolerability | Methylphenidate | OR=4.82 (0.98-23.63) | PBO/Sham | 4/215 | L |
| Autism spectrum disorder | | | | | |
| *Pharmacological interventions* | | | | | |
| Efficacy: inappropriate speech (mixed-rated) | Aripiprazole | SMD=–0.30 (–0.50 to –0.09) | PBO/Sham | 3/400 | L |
| Efficacy: stereotypic (mixed-rated) | Aripiprazole  Methylphenidate  Atomoxetine | SMD=–0.32 (–0.53 to–0.12)  SMD=-0.18 (-0.46 to 0.11)  SMD=-0.16 (-0.50 to 0.18) | PBO/Sham  PBO/Sham  PBO/Sham | 3/400  5/127  4/281 | M  M  L |
| Efficacy: overall (teacher-rated) | Methylphenidate | SMD=–0.53 (–1.26 to 0.19) | PBO/Sham | 2/37 | L |
| Efficacy: social interaction (parent-rated) | Methylphenidate | SMD=–0.21 (–0.6 to 0.18) | PBO/Sham | 2/90 | L |
| Efficacy: social interaction (teacher-rated) | Methylphenidate | SMD=–0.51 (–1.07 to 0.05) | PBO/Sham | 3/103 | L |
| Efficacy: stereotypic (parent-rated) | Methylphenidate | SMD=–0.34 (–0.84 to 0.17) | PBO/Sham | 3/NR | L |
| Efficacy: social withdrawal (mixed-rated) | Aripiprazole | SMD=–0.13 (–0.33 to 0.08) | PBO/Sham | 3/400 | M |
| Response | Risperidone  Aripiprazole | OR=2.57 (1.35-4.86)  RR=2.08 (1.24-3.46) | PBO/Sham  PBO/Sham | 3/241  3/400 | L  L |
| Aggressive behavior | Risperidone  Aripiprazole  Valproate  Lurasidone | SMD=–0.29 (–0.48 to –0.11)  SMD=–0.24 (–0.40 to –0.08)  SMD=–0.18 (–0.71 to 0.35)  SMD=–0.05 (–0.27 to 0.18) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 8/878  8/878  2/57  8/878 | L  L  M  L |
| Acceptability | Risperidone  Antipsychotics  Aripiprazole  Haloperidol  Mood stabilizers | RR=0.52 (0.32-0.86)  RR=0.61 (0.48-0.78)  RR=0.67 (0.49-0.90)  RR=0.80 (0.24-2.62)  RR=1.27 (0.53-3.06) | PBO/sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 6/379  15/1,124  5/526  2/60  5/125 | M  M  M  M  M |
| Tolerability | Risperidone  Antipsychotics  Mood stabilizers  Aripiprazole | RR=0.71 (0.17-2.92)  RR=0.99 (0.55-1.79)  RR=1.13 (0.36-3.53)  RR=1.24 (0.57-2.71) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 5/339  12/1,010  4/112  4/493 | M  M  M  M |
| Discontinuation due to inefficacy | Mood stabilizers | RR=2.11 (0.36-12.42) | PBO/Sham | 3/60 | M |
| Global illness severity | Aripiprazole  Risperidone  Mood stabilizers | SMD=–0.54 (–0.77 to –0.32)  OR=10.5 (4.80-22.60)  RR=1.55 (0.39-6.21) | PBO/Sham  PBO/Sham  PBO/Sham | 3/400  6/446  3/77 | M  L  L |
| Relapse | Risperidone | RR=0.30 (0.13-0.68) | PBO/Sham | 2/56 | M |
| *Psychosocial interventions* | | | | | |
| Efficacy: emotion recognition (mixed-rated) | Computer-assisted interaction  Social skills training | SMD=–0.53 (–1.12 to 0.05)  SMD=–0.34 (–0.88 to 0.20) | WL/NT  WL/NT | 2/48  2/54 | L  L |
| Efficacy: social competence (mixed-rated) | Social skills training | SMD=–0.47 (–0.78 to –0.16) | WL/NT | 4/178 | L |
| Anxiety (subject-rated) | Cognitive behavioral therapy | SMD=–0.61 (–1.54 to 0.33) | WL/NT | 5/181 | L |
| Anxiety (parent-rated) | Cognitive behavioral therapy | SMD=–1.12 (–1.91 to –0.34) | WL/NT | 7/244 | L |
| Functioning: joint attention | Skills training-joint attention | SMD=-0.66 (-0.93 to -0.40) | WL/NT | 9/417 | L |
| Disruptive behavior/dissocial/conduct disorders (with or without ADHD) | | | | | |
| *Pharmacological interventions* | | | | | |
| Efficacy (clinician-rated) | Risperidone | SMD=–0.48 (–0.71 to –0.24) | PBO/Sham | 4/293 | L |
| Efficacy (parent-rated) | Risperidone | SMD=–0.79 (–1.06 to –0.52) | PBO/Sham | 2/225 | M |
| Efficacy (mixed-rated) | Risperidone | SMD=–0.32 (–0.49 to –0.16) | PBO/Sham | 4/590 | M |
| Response: aggressive behavior | Valproate  Lithium | OR=15.6 (1.91-128.1)  RR=4.56 (1.97-10.56) | PBO/Sham  PBO/Sham | 2/47  3/116 | L  L |
| Aggressive behavior (clinician-rated) | Mixed (risperidone, quetiapine) | SMD=–0.24 (–0.76 to 0.29) | PBO/Sham | 2/57 | L |
| Aggressive behavior (parent-rated) | Risperidone | SMD=–0.72 (–0.99 to –0.46) | PBO/Sham | 3/238 | M |
| Aggressive behavior (mixed-rated) | Risperidone  Mixed (risperidone, lithium, methylphenidate) | SMD=–0.60 (–0.89 to –0.31)  SMD=–1.93 (–3.88 to 0.02) | PBO/Sham  PBO/Sham | 2/188  4/172 | L  L |
| Acceptability | Mixed (risperidone, lithium, methylphenidate) | RR= 0.97 (0.60-1.55) | PBO/Sham | 8/631 | L |
| Global illness severity | Risperidone  Mixed (risperidone, quetiapine)  Mixed (carbamazepine, lithium, amphetamines) | SMD=–1.31 (–1.88 to –0.74)  SMD=–0.30 (–0.49 to –0.12)  RR= 2.39 (1.10-5.21) | PBO/Sham  PBO/Sham  PBO/Sham | 2/58  5/435  4/136 | L  M  L |
| *Psychosocial interventions* | | | | | |
| Efficacy (parent-rated) | BI | SMD=–1.00 (–1.68 to –0.32) | WL/NT | 3/207 | L |
| Intellectual disabilities and disruptive behavior/dissocial disorders (with or without ADHD) | | | | | |
| Aggressive behavior (clinician-rated) | Risperidone  Aripiprazole  Valproate | SMD=–1.09 (–1.39 to –0.79)  SMD=–0.64 (–0.91 to –0.36)  SMD=–0.06 (–0.75 to 0.63) | PBO/Sham PBO/Sham  PBO/Sham | 4/257  2/308  2/57 | L  L  L |
| Aggressive behavior (mixed-rated) | Risperidone | SMD=–0.70 (–1.01 to –0.39)94 | PBO/Sham | 3/266 | L |
| Developmental coordination disorders | | | | | |
| Efficacy | Skills training | SMD=–0.27 (–0.85 to 0.31) | WL/NT | 2/51 | L |
| Tic disorder | | | | | |
| Efficacy: tics (clinician-rated) | Desipramine  Methylphenidate | SMD=–0.44 (–0.91 to 0.02)  SMD=–0.28 (–0.58 to 0.03) | PBO/Sham  PBO/Sham | 2/75  4/191 | L  L |
| Tourette's syndrome | | | | | |
| Efficacy (clinician-rated) | Antipsychotics (haloperidol, pimozide, risperidone, ziprasidone)  Guanfacine  Methylphenidate | SMD=–0.74 (–1.08 to –0.41)  SMD=–0.73 (–1.26 to –0.20)  SMD=–0.17 (–0.46 to 0.11) | PBO/Sham  PBO/Sham  PBO/Sham | 4/75  2/58  4/161 | L  L  L |

SMD – standardized mean difference, OR – odds ratio, RR – risk ratio, PBO – placebo, WL – waiting list, NT – no treatment, NR – not recorded, Q – quality (H – high, M – medium, L – low), BI – combination of parental and child behavioral interventions. Bold prints indicate significant values. SMDs<0 indicate intervention is more effective than control. For discontinuation outcomes (acceptability, tolerability, inefficacy) and relapse, OR/RR<1 favors the intervention. For response and remission, OR/RR>1 favors the intervention.

Table 3 Efficacy and effectiveness of pharmacological, psychosocial and brain stimulation interventions vs. inactive control in children/adolescents with schizophrenia spectrum, depressive, and bipolar disorders

| Outcome | Intervention | Effect size (95% CI) | Control | Number of RCTs/patients | Q |
| --- | --- | --- | --- | --- | --- |
| Schizophrenia spectrum disorders | | | | | |
| Efficacy (clinician-rated) | Olanzapine  Risperidone  Lurasidone  Aripiprazole  Quetiapine  Paliperidone  Asenapine  Ziprasidone | SMD=–0.74 (–1.05 to –0.44)  SMD=–0.62 (–0.89 to –0.34)  SMD=–0.48 (–0.71 to –0.25)  SMD=–0.43 (–0.63 to –0.24)  SMD=–0.42 (–0.65 to –0.19)  SMD=–0.42 (–0.66 to –0.18)  SMD=–0.38 (–0.66 to –0.11)  SMD=–0.14 (–0.40 to 0.11) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 28/3,003  28/3,003  28/3,003  28/3,003  28/3,003  28/3,003  28/3,003  28/3,003 | L  L  M  M  M  L  M  L |
| Response | Risperidone  Olanzapine  Lurasidone  Paliperidone  Quetiapine  Asenapine | OR=3.46 (1.92-6.23)  OR=2.64 (1.07-4.18)  OR=2.56 (1.45-4.48)  OR=2.12 (1.07-4.18)  OR=1.86 (1.03-3.32)  OR=1.73 (0.96-3.10) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 28/3,003  28/3,003  28/3,003  28/3,003  28/3,003  28/3,003 | L  L  M  L  M  M |
| Global illness severity | Olanzapine  Risperidone  Paliperidone  Lurasidone  Quetiapine  Ziprasidone  Aripiprazole  Asenapine | SMD=–0.6 (–1.18 to –0.02)  SMD=–0.50 (–0.73 to –0.27)  SMD=–0.44 (–0.67 to –0.22)  SMD=–0.41 (–0.77 to –0.05)  SMD=–0.41 (–0.77 to –0.05)  SMD=–0.40 (–0.68 to –0.12)  SMD=–0.35 (–0.59 to –0.11)  SMD=–0.29 (–0.53 to –0.06) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 13/2,210  12/2,158  12/2,158  13/2,210  13/2,210  13/2,210  13/2,210  13/2,210 | M  L  L  M  M  M  M  M |
| Acceptability | Paliperidone  Risperidone  Olanzapine  Lurasidone  Ziprasidone  Quetiapine  Asenapine  Aripiprazole | OR=0.26 (0.08-0.80)  OR=0.31 (0.14-0.72)  OR=0.36 (0.15-0.85)  OR=0.53 (0.18-1.55)  OR=0.59 (0.22-1.58)  OR=0.63 (0.27-1.43)  OR=0.91 (0.33-2.56)  OR=1.48 (0.60-3.67) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 28/3,003  28/3,003  28/3,003  28/3,003  28/3,003  28/3,003  28/3,003  28/3,003 | L  L  L  M  L  M  M  M |
| Tolerability | Lurasidone  Ziprasidone  Risperidone  Aripiprazole  Asenapine  Quetiapine  Olanzapine  Paliperidone | OR=0.45 (0.16-1.22)  OR=0.99 (0.45-2.30)  OR=2.38 (0.57-13.56)  OR=2.54 (0.70-14.48)  OR=2.67 (0.82-12.47)  OR=3.29 (0.92-16.75)  OR=7.76 (1.23-87.44)  OR=23.12(2.38-778.70) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 13/2,210  13/2,210  13/2,210  13/2,210  13/2,210  13/2,210  13/2,210  13/2,210 | M  M  M  M  M  M  M  M |
| Discontinuation due to inefficacy | Paliperidone  Olanzapine  Risperidone  Ziprasidone  Lurasidone  Asenapine | OR=0.10 (0.04-0.28)  OR=0.14 (0.06-0.31)  OR=0.17 (0.07-0.42)  OR=0.41 (0.20-0.84)  OR=0.39 (0.09-1.77)  OR=0.63 (0.23-1.73) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 28/3,003  28/3,003  28/3,003  28/3,003  28/3,003  28/3,003 | L  L  L  L  M  M |
| Depressive disorders | | | | | |
| *Pharmacological interventions* | | | | | |
| Efficacy (clinician-rated) | Fluoxetine  Desipramine  Duloxetine  Venlafaxine  Mirtazapine  Citalopram  Escitalopram  Paroxetine  Nefazodone  Desvenlafaxine  Sertraline  Imipramine  Vilazodone  Amitriptyline  Nortriptyline | SMD=–0.51(–0.84 to –0.18)  SMD=–0.43 (–1.26 to 0.39)  SMD = –0.22 (–0.85 to 0.42)  SMD = –0.25 (–0.87 to 0.36)  SMD = –0.23 (–0.97 to 0.51)  SMD=–0.18 (–0.89 to 0.55)  SMD=–0.17 (–0.88 to 0.54)  SMD=–0.16 (–0.67 to 0.35)  SMD=–0.14 (–0.85 to 0.57)  SMD=–0.12 (–0.79 to 0.54)  SMD=–0.11 (–0.71 to 0.49)  SMD=–0.03 (–0.75 to 0.68)  SMD=–0.09 (–1.09 to 0.90)  SMD=0.08 (–1.11 to 1.27)  SMD= 1.14 (0.46-1.81) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 70/8,906  70/8,906  70/8,906  70/8,906  70/8,906  70/8,906  70/8,906  70/8,906  70/8,906  70/8,906  70/8,906  70/8,906  70/8,906  70/8,906  70/8,906 | M  M  M  M  M  M  M  M  M  M  M  M  M  M  M |
| Response | Nefazodone  Duloxetine  Fluoxetine  Desipramine  Escitalopram  Sertraline  Paroxetine  Venlafaxine  Citalopram  Imipramine  Nortriptyline  Amitriptyline | OR=2.1 (1.06-4.89)  OR=1.74 (1.12-2.84)  OR=1.70 (1.25-2.39)  OR=1.59 (0.67-4.84)  OR=1.53 (0.96-2.58)  OR=1.44 (0.79-2.97)  OR=1.3 (0.89-1.99)  OR=1.16 (0.72-2.03)  OR=1.02 (0.62-1.82)  OR=0.83 (0.48-1.54)  OR=0.57 (0.24-1.64)  OR=0.22 (0.05-2.78) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260 | M  M  M  M  M  M  M  M  M  M  M  M |
| Acceptability | Nefazodone  Vilazodone  Nortriptyline  Fluoxetine  Mirtazapine  Desvenlafaxine  Citalopram  Duloxetine  Venlafaxine  Amitriptyline  Paroxetine  Escitalopram  Sertraline  Desipramine  Imipramine | OR=0.49 (0.21-1.39)  OR=0.59 (0.27-1.54)  OR=0.76 (0.28-3.41)  OR=0.78 (0.56-1.15)  OR=0.83 (0.40-2.08)  OR=0.85 (0.47-1.74)  OR=0.96 (0.52-1.97)  OR=1.04 (0.62-1.96)  OR=1.12 (0.53-2.70)  OR=1.16 (0.29-12.13)  OR=1.3 (0.81-2.27)  OR=1.4 (0.77-2.86)  OR=162 (0.83-3.22)  OR=2.21 (0.88-7.67)  OR=2.51 (1.26-6.25) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 66/9,075  66/9,075  66/9,075  66/9,075  66/9,075  66/9,075  66/9,075  66/9,075  66/9,075  66/9,075  66/9,075  66/9,075  66/9,075  66/9,075  66/9,075 | M  M  M  M  M  M  M  M  M  M  M  M  M  M  M |
| Tolerability | Amitriptyline  Fluoxetine  Citalopram  Nefazodone  Mirtazapine  Paroxetine  Escitalopram  Desipramine  Sertraline  Duloxetine  Venlafaxine  Imipramine | OR=0.10 (0.02-32.16)  OR=1.03 (0.5-2.7)  OR=1.13 (0.45-3.66)  OR=1.29 (0.3-21.89)  OR=1.36 (0.41-10.99)  OR=1.59 (0.77-3.95)  OR=1.64 (0.46-13.49)  OR=2.85 (0.83-21.8)  OR=2.94 (0.94-17.19)  OR=2.80 (1.20-9.42)  OR=3.19 (1.01-18.7)  OR=5.49 (1.96-20.86) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260  34/5,260 | M  M  M  M  M  M  M  M  M  M  M  M |
| Quality of life | Mixed (fluoxetine, paroxetine, sertraline) | SMD=–0.11 (–0.26 to 0.03) | PBO/Sham | 3/765 | M |
| Relapse | SSRIs | OR=0.34 (0.18-0.64) | PBO/Sham | 3/164 | L |
| Remission | Fluoxetine  Sertraline | RR=1.82 (1.25-2.63)  RR=1.09 (0.72-1.61) | PBO/Sham  PBO/Sham | 2/315  2/376 | M  M |
| Suicide behavior/ ideation | Nefazodone  Mirtazapine  Imipramine  Desvenlafaxine  Escitalopram  Duloxetine  Fluoxetine  Paroxetine  Citalopram  Vilazodone  Sertraline  Venlafaxine | OR=0.29 (0.06-6.31)  OR=0.53 (0.10-40.83)  OR=0.59 (0.19-3.07)  OR=0.74 (0.41-1.49)  OR=0.94 (0.44-2.55)  OR=0.93 (0.55-1.71)  OR=1.11 (0.74-1.75)  OR=1.71 (0.81-5.05)  OR=1.18 (0.46-4.43)  OR=1.96 (0.45-100.00)  OR=2.22 (0.75-12.5)  OR=8.33 (1.92-NC) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 34/NR  34/NR  34/NR  34/NR  34/NR  34/NR  34/NR  34/NR  34/NR  34/NR  34/NR  34/NR | M  M  M  M  M  M  M  M  M  M  M  M |
| *Psychosocial interventions* | | | | | |
| Efficacy (clinician-rated) | IPT  PSOLV  FT  CBT  IPT  FT  CBT  PSD-O | SMD=–1.37 (–2.04 to –0.7)  SMD=–1.26(–2.48 to –0.03)  SMD=–1.03 (–1.66 to –0.4)  SMD=–0.94(–1.40 to –0.48)  SMD=–0.70 (–1.29 to –0.12)  SMD=–0.36 (–0.95 to 0.24)  SMD=–0.27 (–0.72 to 0.18)  SMD=0.08 (–0.67 to 0.84) | WL/NT  WL/NT  WL/NT  WL/NT  PBO/Sham  PBO/Sham PBO/Sham  PBO/Sham | 70/8,906  70/8,906  70/8,906  70/8,906  70/8,906  70/8,906  70/8,906  70/8,906 | L  L  L  L  L  L  L  L |
| Response | PSD-O | RR=1.68 (1.08 -2.63) | WL/PBO/Sham | 2/83 | L |
| Acceptability | IPT  IPT  CBT  PSOLV  CBT  FT  PSD-O  BT | OR=0.53 (0.20-1.15)  OR=0.65 (0.19-1.62)  OR=0.65 (0.32-1.16)  OR=0.77 (0.01-4.40)  OR=0.77 (0.34-1.48)  OR=0.84 (0.35-1.72)  OR=0.96 (0.37-1.93)  OR=1.27 (0.19-4.32) | PBO/Sham  WL/NT  PBO/Sham  WL/NT  WL/NT  PBO/Sham  PBO/Sham PBO/Sham | 66/9,075  66/9,075  66/9,075  66/9,075  66/9,075  66/9,075  66/9,075  66/9,075 | M  M  M  M  M  M  M  M |
| Suicide attempt/ideation | IPT  CBT  PSD-O | OR=0.64 (0.04-2.59)  OR=11.31 (0.01-46.11)  OR=8.64 (0.01-40.05) | PBO/Sham  PBO/Sham  PBO/Sham | 34/NR  34/NR  34/NR | M  M  M |
| *Combination interventions* | | | | | |
| Efficacy (clinician-rated) | Fluoxetine+  CBT | SMD=–0.73(–1.39 to –0.07) | PBO/Sham | 70/8,906 | M |
| Acceptability | Fluoxetine+  CBT | OR=0.75 (0.39-1.65) | PBO/Sham | 66/9,075 | M |
| Suicide attempt/ideation | Fluoxetine+  CBT | OR=0.88 (0.41-2.35) | PBO/Sham | 34/NR | M |
| Bipolar disorder, depressive episode | | | | | |
| Efficacy (clinician-rated) | Quetiapine | SMD=–0.10 (–0.32 to 0.13) | PBO/Sham | 2/224 | M |
| Response | Quetiapine | RR=1.1 (0.89-1.35) | PBO/Sham | 3/250 | L |
| Acceptability | Quetiapine | RR=0.73 (0.36-1.49) | PBO/Sham | 2/225 | L |
| Global illness severity | Quetiapine | SMD=–0.20 (–0.46 to –0.06) | PBO/Sham | 2/224 | M |
| Remission | Quetiapine | RR=1.23 (0.90-1.68) | PBO/Sham | 3/250 | L |
| Tolerability | Quetiapine | RR=0.31 (0.11-1.01) | PBO/Sham | 2/225 | L |
| Bipolar disorder, manic episode | | | | | |
| Efficacy (clinician  -rated) | Aripiprazole | SMD=–1.08 (–1.32 to –0.85) | PBO/Sham | 2/339 | M |
| Response | Mixed (mood stabilizers and antipsychotics)  Aripiprazole  SGAs  Mood stabilizers | OR=2.24 (z=8.12, p<0.001)  RR=1.86 (1.43-2.43)  Z=10.34, p<0.001  Z=2.06, p=0.04 | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 9/1,362  2/332  6/1,190  2/172 | M  M  H  M |
| Acceptability | Aripiprazole  Valproate | RR=0.80 (0.51-1.27)  OR=1.77 (0.83-3.78) | PBO/Sham  PBO/Sham | 2/339  2/179 | M  M |
| Tolerability | Aripiprazole | RR=5.19 (0.92-29.25) | PBO/Sham | 2/339 | M |
| Discontinuation due to inefficacy | Aripiprazole | RR=0.27 (0.09-0.82) | PBO/Sham | 2/339 | M |

SMD – standardized mean difference, OR – odds ratio, RR – risk ratio, PBO – placebo, WL – waiting list, NT – no treatment, Q – quality (H – high, M – medium, L – low), BT – behavioral therapy, CBT – cognitive behavioral therapy, FT – family therapy, IPT – interpersonal therapy, PSD-O – psychodynamic-oriented, PSOLV – problem solving, SSRIs – selective serotonin reuptake inhibitors, SGAs – second-generation antipsychotics. Bold prints indicate significant values. SMDs<0 indicate intervention is more effective than control. For discontinuation outcomes (acceptability, tolerability, inefficacy) and relapse, OR/RR<1 favors the intervention. For response and remission, OR/RR>1 favors the intervention.

Table 4 Efficacy and effectiveness of pharmacological, psychosocial and brain stimulation interventions vs. inactive control in children/adolescents with anxiety, obsessive-compulsive, stress-related, and mixed disorders

| Outcome | Intervention | Effect size (95% CI) | Control | Number of RCTs/  patients | Q |
| --- | --- | --- | --- | --- | --- |
| Anxiety disorders | | | | | |
| *Pharmacological interventions* | | | | | |
| Efficacy (clinician  -rated) | Paroxetine  Fluvoxamine  Imipramine  Guanfacine  Fluoxetine  Atomoxetine  Duloxetine  Sertraline  Venlafaxine | SMD=–0.43 (–0.75 to –0.10)  SMD=–0.36 (–0.61 to –0.10)  SMD=–0.27 (–0.92 to 0.39)  SMD=–0.13 (–0.39 to 0.12)  SMD=–0.11 (–0.33 to 0.12)  SMD=–0.11 (–0.38 to 0.16)  SMD=–0.09 (–0.27 to 0.09)  SMD=–0.08 (–0.25 to 0.09)  SMD=–0.06 (–0.22 to 0.04) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 14/2,502  14/2,502  14/2,502  14/2,502  14/2,502  14/2,502  14/2,502  14/2,502  14/2,502 | M  M  M  M  M  M  M  M  M |
| Efficacy (subject-rated) | Fluoxetine  SNRIs  Venlafaxine  SSRIs  Atomoxetine  TCAs | SMD=–0.51 (–0.85 to –0.18)  SMD=–2.14 (–9.75 to 5.48)  SMD=–1.71 (–3.93 to 0.51)  SMD=–0.42 (–0.96 to 0.12)  SMD=–0.29 (–0.51 to 0.08)  SMD= 0.36 (–0.27 to 0.99) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 2/154  3/622  2/443  4/197  2/331  2/41 | M  M  M  M  M  M |
| Efficacy (parent-rated) | SSRIs | SMD=–0.82 (–1.38 to –0.27) | PBO/Sham | 2/96 | L |
| Response | Fluvoxamine  Sertraline  Fluoxetine  Guanfacine  Atomoxetine  Paroxetine  Imipramine  Venlafaxine  Duloxetine  Clomipramine | OR=8.17 (1.35-49.40)  OR=6.05 (2.23-49.40)  OR=4.06 (1.49-18.17)  OR=5.47 (0.74-49.40)  OR=4.06 (0.67-24.53)  OR=3.67 (0.67-20.09)  OR=3.00 (0.61-14.88)  OR=2.46 (0.90-6.69)  OR=2.01 (0.37-11.02)  OR=1.22 (0.22-6.69) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 19/2,656  19/2,656  19/2,656  19/2,656  19/2,656  19/2,656  19/2,656  19/2,656  19/2,656  19/2,656 | M  M  M  M  M  M  M  M  M  M |
| Acceptability | Clomipramine  Paroxetine  Fluvoxamine  Sertraline  Guanfacine  Atomoxetine  Duloxetine  Venlafaxine  Fluoxetine  Imipramine | OR=0.55 (0.02-7.39)  OR=0.61 (0.12-3.32)  OR=0.67 (0.11-4.06)  OR=0.67 (0.14-2.72)  OR=0.67 (0.10-4.95)  OR=0.82 (0.15-4.95)  OR=1.00 (0.18-5.47)  OR=1.11 (0.33-3.67)  OR=1.65 (0.50-6.69)  OR=2.01 (0.37-9.97) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 20/2,679  20/2,679  20/2,679  20/2,679  20/2,679  20/2,679  20/2,679  20/2,679  20/2,679  20/2,679 | M  M  M  M  M  M  M  M  M  M |
| Remission | Fluoxetine | RR=2.52 (1.19-5.32) | PBO/Sham | 2/95 | L |
| Suicide attempt/  ideation | Sertraline  Duloxetine  Venlafaxine  Atomoxetine  Guanfacine  Imipramine  Paroxetine | LogOR=-19.8 (-61.7 to 0.7)  LogOR=0.2 (-2.5 to 2.8)  LogOR=1.4 (-1.4 to 5.24)  LogOR=6.6 (-31.6 to 22.7)  LogOR=16.1 (-1.0 to 58.3)  LogOR=17.3 (-0.1 to 54.8)  LogOR=20.0 (1.7 to 60.47) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 9/1,648  9/1,648  9/1,648  9/1,648  9/1,648  9/1,648  9/1,648 | M  M  M  M  M  M  M |
| Tolerability | Venlafaxine  Atomoxetine  Duloxetine  Sertraline  Paroxetine  Fluovoxamine  Fluoxetine  Imipramine  Guanfacine | LogOR=–0.8 (–3.8 to 2.1)  LogOR=0.0 (–5.3 to 5.3)  LogOR=0.2 (–3.9 to 4.3)  LogOR=1.7 (–2.8 to 6.6)  LogOR=1.7 (–2.5 to 6.0)  LogOR=2.1 (–2.4 to 7.0)  LogOR=2.5 (–1.8 to 7.9)  LogOR=16.6 (–37.5 to 83.7)  LogOR=29.2 (2.2-94.3) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 15/2,516  15/2,516  15/2,516  15/2,516  15/2,516  15/2,516  15/2,516  15/2,516  15/2,516 | M  M  M  M  M  M  M  M  M |
| *Psychosocial interventions* | | | | | |
| Efficacy (clinician  -rated) | CBT/BT | SMD=–0.85 (–1.12 to –0.57) | WL/NT | 7/358 | L |
| Efficacy (subject-rated) | CBT-Child only  CBT-Group  CBT  CBT-Child+P  CBT-Individual  CBT  CBT-Parent only | SMD=–1.04 (–1.41 to –0.67)  SMD=–0.91 (–1.22 to –0.60)  SMD=–0.67 (–0.88 to –0.47)  SMD=–0.45 (–0.67 to –0.23)  SMD=–0.39 (–0.64 to –0.15)  SMD=–0.31 (–0.51 to –0.11)  SMD=0.04 (–0.38 to 0.46) | WL/NT  WL/NT  WL/NT  WL/NT  WL/NT  PBO/Sham  WL/NT | 24/1,239  27/1,268  45/2,831  20/1,285  21/1,203  15/978  5/307 | L  L  L  L  L  L  L |
| Efficacy (parent-rated) | CBT-Group  CBT-Child only  CBT  CBT-Child+P  CBT-Individual  CBT-Parent only  CBT | SMD=–0.92 (–1.21 to –0.62)  SMD=–0.87 (–1.21 to –0.53)  SMD=–0.70 (–0.90 to –0.51)  SMD=–0.69 (–0.98 to –0.39)  SMD=–0.43 (–0.65 to –0.21)  SMD=–0.37 (–0.77 to 0.04)  SMD=–0.25 (–0.61 to 0.11) | WL/NT  WL/NT  WL/NT  WL/NT  WL/NT  WL/NT  PBO/Sham | 21/1,279  13/734  35/2137  17/1,031  17/858  5/372  8/638 | L  L  L  L  L  L  L |
| Efficacy (mixed-rated) | BT-Group  CBT-Group  BT-Individual+P  CBT-Group+P  CBT-Individual  CBT-Individual+P  CBT-Group  CBT-Parent only  CBT-Internet  BT-Individual+Group  CBT-Individual+Group  BT-Individual+P  CBT-Group+P  CBT-Individual  CBT-Individual+P  BT-Individual+Group  CBT-Internet | SMD=–1.43 (–2.36 to –0.51)  SMD=–1.43 (–1.76 to –1.09)  SMD=–1.09 (–1.93 to –0.25)  SMD=–0.99 (–1.31 to –0.68)  SMD=–0.99 (–1.30 to –0.68)  SMD=–0.84 (–1.16 to –0.53)  SMD=–0.76 (–1.16 to –0.36)  SMD=–0.70 (–1.22 to –0.19)  SMD=–0.61 (–1.02 to –0.20)  SMD=–0.73 (–1.59 to 0.13)  SMD=–0.64 (–1.69 to 0.41)  SMD=–0.42 (–1.29 to 0.44)  SMD=–0.33 (–0.78 to 0.13)  SMD=–0.32 (–0.72 to 0.07)  SMD=–0.18 (–0.61 to 0.25)  SMD=–0.06 (–0.94 to 0.82)  SMD=0.06 (–0.48 to 0.60) | WL/NT  WL/NT  WL/NT  WL/NT  WL/NT  WL/NT  PBO/Sham  WL/NT  WL/NT  WL/NT  WL/NT  PBO/Sham PBO/Sham  PBO/Sham PBO/Sham  PBO/Sham PBO/Sham | 101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625 | L  L  L  L  L  L  L  L  L  L  L  L  L  L  L  L  L |
| Acceptability | CBT-Individual+Group  BT-Individual+P  BT-Individual+P  CBT-Group+P  CBT-Group  BT  CBT-Individual  CBT-Group  CBT  CBT-Group+P  CBT  CBT-Internet  CBT-Individual  CBT-Internet  CBT-Individual+P  BT-Individual+Group  BT-Group  CBT-Individual+P  CBT-Parent only | OR=0.26 (0.05-5.73)  OR=0.64 (0.22-2.72)  OR=0.81 (0.19-2.27)  OR=0.90 (0.46-1.60)  OR=0.85 (0.46-1.44)  OR=0.90 (0.32-3.95)  OR=0.92 (0.52-1.52)  OR=0.93 (0.57-1.63)  OR=1.09 (0.85-1.41)  OR=0.99 (0.67-1.55)  OR=1.00 (0.68-1.49)  OR=1.02 (0.42-2.08)  OR=1.02 (0.67-1.67)  OR=1.05 (0.59-2.05)  OR=1.11 (0.60-1.90)  OR=1.13 (0.28-3.19)  OR=1.21 (0.27-22.51)  OR=1.23 (0.80-2.02)  OR=1.43 (0.75-3.15) | WL/NT  WL/NT  PBO/Sham PBO/Sham  PBO/Sham  WL/NT  PBO/Sham  WL/NT  WL/NT  WL/NT  PBO/Sham PBO/Sham  WL/NT  WL/NT  PBO/Sham PBO/Sham  WL/NT  WL/NT  WL/NT | 101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  45/3,158  101/6,625  12/797  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625 | L  L  L  L  L  M  L  L  L  M  L  L  L  L  L  L  L  L  L |
| Depressive symptoms | CBT  CBT | SMD=–0.34 (–0.51 to –0.17)  SMD=–0.18 (–0.45 to 0.09) | WL/NT  PBO/Sham | 17/1,157  10/613 | L  L |
| Functioning | CBT | SMD=–1.03 (–1.38 to –0.68) | WL/NT | 11/557 | L |
| Quality of life | CBT-Parent only  CBT-Individual  CBT-Individual  CBT-Internet  CBT-Group  CBT-Individual+P  CBT-Group+P  CBT-Group  CBT-Internet  BT-Individual+Group  BT-Individual+Group  CBT-Individual+Group | SMD=–1.87 (–3.04 to –0.71)  SMD=–1.13 (–1.82 to –0.45)  SMD=–1.01 (–1.55 to –0.48)  SMD=–0.86 (–1.57 to –0.15)  SMD=–0.85 (–1.45 to –0.26)  SMD=–0.80 (–1.33 to –0.27)  SMD=–0.75 (–1.34 to –0.17)  SMD=–0.73 (–1.34 to –0.11)  SMD=–0.73 (–1.14 to –0.33)  SMD=–0.79 (–1.68 to 0.09)  SMD=–0.67 (–1.56 to 0.21)  SMD=–0.55 (–1.78 to 0.69) | WL/NT  PBO/Sham  WL/NT  PBO/Sham PBO/Sham  WL/NT  WL/NT  WL/NT  PBO/Sham  WL/NT  WL/NT  WL/NT | 101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625  101/6,625 | L  L  L  L  L  L  L  L  L  L  L  L |
| Remission | CBT-Child only  CBT-Group  CBT-Remote  CBT  CBT-Individual  CBT-Individual+P  CBT-Child only  CBT-Group  CBT-Parent only  CBT  CBT-Individual  CBT-Individual+P | OR=10.42 (5.84-7.60)  OR=6.25 (4.45-8.78)  OR=6.14 (2.97-12.71)  OR=5.45 (3.90-7.60)  OR=4.53 (2.55-8.03)  OR=4.08 (2.72-6.11)  OR=3.58 (1.92-6.65)  OR=3.10 (1.14-8.45)  OR=2.83 (1.12-7.16)  OR=2.28 (1.33-3.89)  OR=2.04 (1.06-3.91)  OR=1.12 (0.65-1.92) | WL/NT  WL/NT  WL/NT  WL/NT  WL/NT  WL/NT  PBO/Sham PBO/Sham  WL/NT  PBO/Sham PBO/Sham  PBO/Sham | 19/1,184  25/1,532  10/591  39/2,697  17/1,165  19/1,142  7/509  5/353  4/371  10/822  5/469  4/313 | M  M  L  L  L  M  L  L  L  L  L  L |
| Social anxiety disorder | | | | | |
| Efficacy (subject-rated) | CBT  BT  CBT  CBT-Group  CBT/BT  CBT+P  CBT-Individual  CBT-Individual+Group  CBT-Child only  CBT-Internet | SMD=–1.59 (–2.33 to –0.86)  SMD=–1.22 (–2.06 to –0.38)  SMD=–1.19 (–1.72 to –0.67)  SMD=–1.19 (–1.93 to –0.45)  SMD=–1.13 (–1.59 to –0.68)  SMD=–1.13 (–1.59 to –0.67)  SMD=–1.10 (–1.91 to –0.29)  SMD=–0.80 (–1.19 to –0.41)  SMD=–0.75 (–1.24 to –0.26)  SMD=–0.52 (–1.01 to –0.03) | WL/NT  WL/NT/PBO/Sham  WL/NT/PBO/Sham  WL/NT/PBO/Sham  WL/NT/PBO/Sham  WL/NT/PBO/Sham  WL/NT/PBO/Sham  WL/NT/PBO/Sham  WL/NT/PBO/Sham  WL/NT/PBO/Sham | 11/603  4/169  14/872  11/670  17/1,016  17/983  3/127  3/115  2/70  2/143 | L  L  L  L  L  L  L  L  L  L |
| Acceptability | CBT | RR=1.00 (0.72-1.41) | WL/NT/PBO/Sham | 16/1,052 | M |
| Depressive symptoms | CBT/BT | SMD=–0.39 (–0.63 to –0.16) | WL/NT/PBO/Sham | 8/299 | L |
| Quality of life | CBT/BT | SMD=–0.79 (–1.17 to –0.41) | WL/NT/PBO/Sham | 9/552 | L |
| Remission | CBT/BT | RR=8.99 (5.27-15.33) | WL/NT/PBO/Sham | 13/832 | L |
| Obsessive-compulsive disorder | | | | | |
| *Pharmacological interventions* | | | | | |
| Efficacy (clinician  -rated) | Sertraline  Fluoxetine  Clomipramine  Fluvoxamine | SMD=–0.24 (–0.46 to –0.03)  SMD=–0.24 (–0.47 to –0.01)  SMD=–0.31 (–0.64 to 0.02)  SMD=–0.21 (–0.49 to 0.06) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 17/991  17/991  17/991  17/991 | L  L  L  L |
| Response | Fluoxetine  SSRI/TCAs | RR=1.49 (1.15-1.96)  RR=1.80 (1.43-2.26) | PBO/Sham  PBO/Sham | 2/146  7/692 | L  L |
| Acceptability | Fluoxetine  Fluvoxamine  Sertraline  Paroxetine  Clomipramine | MOR=0.74 (0.25-1.68)  MOR=0.79 (0.24-2.07)  MOR=0.89 (0.32-2.07)  MOR=1.12 (0.37-3.42)  MOR=3.06 (0.54-21.69) | PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham  PBO/Sham | 18/1,143  18/1,143  18/1,143  18/1,143  18/1,143 | L  L  L  L  L |
| Tolerability | SSRIs | RR=3.59 (1.89-6.84) | PBO/Sham | 7/807 | L |
| Global illness severity | Fluoxetine  SSRIs | SMD=–0.52 (–0.86 to –0.18) SMD=–0.42 (–0.61 to –0.23) | PBO/Sham  PBO/Sham | 2/1465/556 | L  M |
| Remission | SSRIs | RR=2.06 (1.03-4.13) | PBO/Sham | 3/302 | L |
| *Pharmacological augmentation (in SSRI-refractory cases)* | | | | | |
| Response | Risperidone  Quetiapine  Olanzapine | OR=6.35 (1.48-27.3)  OR=2.33 (0.88-6.20)  OR=2.74 (0.34-21.9) | PBO/Sham  PBO/Sham  PBO/Sham | 3/72  3/102  2/70 | M  M  L |
| *Psychosocial interventions* | | | | | |
| Efficacy (clinician  -rated) | CBT  BT  CBT | SMD=–0.78 (–1.05 to –0.51)  SMD=–0.72 (–1.20 to –0.24)  SMD=–0.23 (–0.56 to 0.11) | WL/NT  WL/NT  PBO/Sham | 17/991  17/991  17/991 | L  L  L |
| Response | CBT/BT-ERP | RR=3.93 (2.52-6.14) | WL/NT/PBO/Sham | 6/236 | L |
| Acceptability | CBT  BT-ERP  CBT  CBT  BT | MOR=0.49 (0.09-2.40)  RR=0.80 (0.35-1.84)  MOR=0.86 (0.23-3.24)  MOR=0.94 (0.21-4.79)  MOR=14.28 (0.87-785.20) | PBO/Sham  PBO/WL  PBO/Sham  WL/NT  WL/NT | 18/1,143  6/301  18/1,143  18/1,143  18/1,143 | L  L  L  L  L |
| Functioning (subject-rated) | CBT | SMD=–1.15 (–2.11 to –0.19) | WL/NT | 3/194 | L |
| Functioning (parent-rated) | CBT  CBT | SMD=–0.95 (–1.61 to –0.28)  SMD=–0.31 (–0.63 to 0.01) | WL/NT  PBO/Sham | 3/194  2/183 | L  L |
| Remission | CBT  CBT | RR=2.33 (1.33-4.00)  RR=1.59 (1.28-1.96) | WL/NT  PBO/Sham | 4/271  3/153 | L  L |
| Quality of life | CBT | SMD=–0.39 (–0.77 to –0.02) | WL/PBO/Sham | 2/223 | L |
| *Combined interventions* | | | | | |
| Efficacy | CBT+sertraline | SMD=–0.58 (–0.91 to –0.25) | PBO/Sham | 17/991 | L |
| Acceptability | CBT+sertraline | MOR=0.54 (0.08-3.15) | PBO/Sham | 18/1,143 | L |
| Post-traumatic stress disorder | | | | | |
| Efficacy | CBT  EMDR  NET | SMD=–1.34 (–1.79 to –0.89)  SMD=–0.61 (–1.96 to 0.74)  SMD=–0.57 (–1.23 to 0.09) | WL/NT  WL/NT  WL/NT | 3/98  2/65  2/79 | L  L  L |
| Response | CBT  NET | OR=8.64 (2.01-37.14)  OR=3.82 (0.67-21.8) | WL/NT  WL/NT | 2/49  2/78 | L  L |
| Acceptability | NET | OR=5.13 (0.56-47.28) | WL/NT | 2/83 | L |
| Anxiety symptoms | NET | SMD=–0.66 (–1.33 to 0.01) | WL/NT | 2/59 | L |
| Depressive symptoms | CBT | SMD=–0.8 (–1.47 to –0.131) | WL/NT | 3/98 | L |
| Enuresis | | | | | |
| *Pharmacological interventions* | | | | | |
| Efficacy | Imipramine | SMD=–0.46 (–0.67 to –0.24) | PBO/Sham | 4/347 | M |
| Response | Amitriptyline  Imipramine | RR=1.22 (1.02-1.45)  RR=1.35 (1.11-1.64) | PBO/Sham  PBO/Sham | 2/98  12/831 | L  L |
| *Psychosocial interventions* | | | | | |
| Efficacy | BT-Alarm | SMD=–1.30 (–2.16 to –0.44) | WL/NT | 4/127 | L |
| Response | BT-Alarm  BT-Alarm  BT-Reward | RR=7.23 (1.40-37.77)  RR=1.59 (1.16-2.17)  RR=1.22 (1.03-1.45) | WL/NT  PBO/Sham  WL/NT | 18/827  2/181  2/325 | L  L  L |

SMD – standardized mean difference, OR – odds ratio, MOR – median odds ratio, RR – risk ratio, PBO – placebo, WL – waiting list, NT – no treatment, Q – quality (H – high, M – medium, L – low), BT – behavioral therapy, BT-ERP – behavioral therapy with exposure and response prevention, CBT – cognitive behavioral therapy, EMDR – eye movement desensitization and reprocessing, NET – narrative exposure therapy, P – parental involvement, SSRIs – selective serotonin reuptake inhibitors, SNRIs, serotonin-norepinephrine reuptake inhibitors, TCAs – tricyclic antidepressants. Bold prints indicate significant values. SMDs<0 indicate intervention is more effective than control. For discontinuation outcomes (acceptability, tolerability, inefficacy) and relapse, OR/RR<1 favors the intervention. For response and remission, OR/RR>1 favors the intervention.

Table 5 Efficacy and effectiveness of pharmacological, psychosocial and brain stimulation interventions vs. treatment as usual (TAU) or low intensity psychosocial intervention (LIP) in children/adolescents (only significant differences are reported)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Outcome | Intervention | Effect size (95% CI) | Control | Number of RCTs/  patients | Q |
| Anxiety disorders | | | | | |
| Efficacy (mixed-  rated) | CBT-Group | SMD=–0.84 (–1.47 to –0.21) | TAU | 101/6,625 | L |
| Functioning | CBT | SMD=–1.06 (–1.57 to –0.55) | TAU/LIP/PBO/Sham | 5/467 | L |
| Remission | CBT-Individual  +P | OR=8.56 (3.10-23.66) | TAU | 5/172 | L |
| Autism spectrum disorder | | | | | |
| Efficacy: overall (mixed-rated) | PCIT | SMD=–0.22 (–0.41 to –0.03) | TAU/LIP | 6/420 | L |
| Efficacy: reciprocity (clinician-rated) | Mixed psychosocial interventions | SMD=–0.53 (–0.78 to –0.29) | TAU | 8/380 | L |
| Cognition: developmental quotient | Mixed psychosocial interventions | SMD=–0.36 (–0.66 to –0.05) | TAU | 5/232 | L |
| Cognition | PCIT | SMD=–0.24 (–0.46 to –0.03) | TAU/LIP | 6/334 | L |
| Anxiety disorder remission | CBT | OR=11.25 (3.11-40.79) | TAU | 4/142 | L |
| Depressive disorders | | | | | |
| Efficacy (clinician  -rated) | IPT | SMD=–0.66 (–1.22 to –0.09) | TAU | 70/8,906 | L |
| Encopresis | | | | | |
| Efficacy: soiling | BT+TAU | SMD=–0.35 (–0.63 to –0.07) | TAU | 4/209 | L |
| Response | BT+TAU | RR=1.78 (1.25-2.55) | TAU | 4/216 | L |
| Obsessive-compulsive disorder | | | | | |
| Response | BT-ERP | RR=1.71 (1.29-2.25) | TAU/LIP | 4/271 | L |
| Acceptability | BT-ERP | RR=0.60 (0.39-0.93) | TAU/LIP | 4/251 | L |

SMD – standardized mean difference, OR – odds ratio, RR – risk ratio, PBO – placebo, Q – quality (H – high, M – medium, L – low), BT – behavioral therapy, BT-ERP – behavioral therapy with exposure and response prevention, CBT – cognitive behavioral therapy, IPT – interpersonal therapy, PCIT – parent-child interaction therapy, P – parental involvement, SMDs<0 indicate intervention is more effective than control. For discontinuation outcomes (acceptability, tolerability, inefficacy) and relapse, OR/RR<1 favors the intervention. For response and remission, OR/RR>1 favors the intervention.

Table 6 Efficacy and effectiveness of pharmacological, psychosocial and brain stimulation interventions vs. active psychological intervention or drug condition in children/adolescents (only significant differences are reported)

| Outcome | Intervention | Effect size (95% CI) | Control | Number of RCTs/  patients | Q |
| --- | --- | --- | --- | --- | --- |
| Anorexia nervosa | | | | | |
| Efficacy: weight gain | FT | SMD=–0.44 (–0.74 to –0.14) | Other than FT | 4/178 | L |
| Anxiety disorders | | | | | |
| Efficacy (mixed-rated) | CBT-Group | SMD=–0.44 (–0.82 to –0.06) | CBT-Individual | 101/6,625 | L |
| Attention-deficit/hyperactivity disorder (ADHD) | | | | | |
| Efficacy (clinician  -rated) | Amphetamines  Methylphenidate | SMD=–0.24 (–0.44 to –0.05)  SMD=–0.22 (–0.39 to –0.05) | Methylphenidate  Atomoxetine | 46/NR  46/NR | H  H |
| Efficacy (parent-rated) | Methylphenidate  Methylphenidate | SMD=–1.07 (–1.74 to –0.40)  SMD=–0.23 (–0.37 to –0.10) | Bupropion  Atomoxetine | 23/NR  23/NR | H  H |
| Response | Methylphenidate | OR=1.44 (1.08-1.92) | Atomoxetine | 113/19,398 | M |
| Aggressive behavior | Amphetamines | SMD=–0.35 (–0.56 to –0.13) | Methylphenidate | 2/132 | L |
| Acceptability | Methylphenidate | OR=0.68 (0.52-0.91) | Atomoxetine | 171/22,961 | M |
| Tolerability | Methylphenidate | OR=0.39 (0.18-0.83) | Guanfacine | 60/12,188 | M |
| Discontinuation due to inefficacy | Amphetamines | OR=0.23 (0.10-0.44) | Atomoxetine | 45/9,087 | M |
| Global illness severity | Amphetamines | OR=3.39 (1.95-5.88) | Atomoxetine | 40/NR | H |
| Efficacy: inattention (mixed-rated) | Neurofeedback | SMD=0.44 (0.02 to 0.86) | Stimulants | 4/161 | L |
| Acceptability | Neurofeedback | OR=0.45 (0.21-0.95) | COG TR | 171/22,961 | M |
| Response | BT+stimulants  BT+stimulants | OR=4.76 (2.50-9.09)  OR=4.58 (2.49-8.75) | BT  Stimulants | 113/19,398  113/19,398 | M  M |
| Autism spectrum disorder | | | | | |
| Efficacy: stereotypic (clinician-rated) | BT-IT | SMD=–0.78 (–1.42 to –0.13) | BT-CI | 2/40 | L |
| Efficacy: distal social behavior (clinician-rated) | BT-IT | SMD=–0.98 (–1.64 to –0.32) | BT-CI | 2/40 | L |
| Bipolar disorder, manic episode | | | | | |
| Efficacy (clinician  -rated) | Risperidone | SMD=–1.01 (–1.29 to –0.74) | Valproate | 2/228 | M |
| Enuresis | | | | | |
| Acceptability | Desmopressin | OR=0.45 (0.29-0.71) | BT-Alarm | 15/1,502 | M |
| Efficacy | BT-Alarm | SMD= –0.43 (–0.77 to –0.08) | Desmopressin | 4/285 | L |
| Relapse | BT-Alarm | OR=0.15 (0.03-0.53) | Desmopressin | 12/1,381 | M |
| Efficacy | Desmopressin+  BT-Alarm | SMD= –0.58 (–0.89 to –0.26) | Desmopressin | 2/156 | L |
| Response | Desmopressin+  anticholinergics  Imipramine+  oxybutynin  Imipramine+  oxybutynin  Desmopressin+  BT-Alarm | OR=2.80 (1.50-5.40)    RR=1.47 (1.09-2.00)    RR=1.46 (1.06-2.01)    RR=1.32 (1.08-1.62) | Desmopressin  Imipramine  Oxybutynin  Desmopressin | 15/1,350  2/101  2/100  5/359 | M  L  L  L |
| Relapse | Oxybutynin+ imipramine  Oxybutynin+ imipramine | RR=0.50 (0.30-0.81)  RR=0.48 (0.31-0.74) | Oxybutynin  Imipramine | 2/81  2/85 | L  L |
| Depressive disorders | | | | | |
| Efficacy (clinician  -rated) | Fluoxetine | SMD=–1.65 (–2.34 to –0.95) | Nortriptyline | 70/8,906 | M |
| Response | Fluoxetine | OR=3.02 (1.04-7.22) | Nortriptyline | 34/5,260 | M |
| Tolerability | Paroxetine  Fluoxetine | OR=0.22 (0.08-0.87)  OR=0.31 (0.13-0.95) | Imipramine  Duloxetine | 34/5,260  34/5,260 | M  M |
| Suicidal ideation | CBT | SMD=–0.27 (–0.51 to –0.03) | SSRIs | 2/268 | L |
| Remission | CBT+SSRI | OR=2.15 (1.15-4.02) | CBT+PBO | 2/173 | M |
| Functioning | CBT+SSRI | SMD=–0.20 (–0.33 to –0.08) | Standalone AD | 4/850 | L |
| Schizophrenia spectrum disorders | | | | | |
| Efficacy (clinician  -rated) | Haloperidol  Clozapine  SGAs | SMD=–1.35 (–2.16 to –0.55)  SMD=–0.86 (–1.54 to –0.17)  SMD=–0.36(–0.56 to –0.16) | Fluphenazine  Olanzapine  FGAs | 28/3,003  28/3,003  4/243 | L  L  L |
| Response | Risperidone | OR=5.53 (2.01-15.18) | Haloperidol | 28/3,003 | L |
| Tic disorder | | | | | |
| Response | Topiramate  Topiramate | RR=1.10 (1.02-1.18)  RR=1.09 (1.01-1.19) | Haloperidol/  tiapride  Haloperidol | 14/1,017  10/727 | M  L |

SMD – standardized mean difference, OR – odds ratio, RR – risk ratio, PBO – placebo, Q – quality (H – high, M – medium, L – low), BT – behavioral therapy, BT-IT– behavioral therapy imitative interaction, BT-CI – behavioral therapy contingency interaction, CBT – cognitive behavioral therapy, FT – family therapy, COG TR - cognitive training, AD – antidepressant, SSRI – selective serotonin reuptake inhibitor, SGAs – second-generation antipsychotics, FGAs – first-generation antipsychotics, NR – not reported. SMDs<0 indicate intervention is more effective than control. For discontinuation outcomes (acceptability, tolerability, inefficacy) and relapse, OR/RR<1 favors the intervention. For response and remission, OR/RR>1 favors the intervention.

Table 7 Efficacy and effectiveness of pharmacological, psychosocial and brain stimulation interventions vs. mixed control conditions in children/adolescents (only significant differences are reported)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Outcome | Intervention | Effect size (95% CI) | Control | Number of RCTs/  patients | Q |
| Attention-deficit/hyperactivity disorder (ADHD) | | | | | |
| Efficacy (mixed-rated) | BI | SMD=–0.55 (–0.77 to –0.32) | WL/AC/LIP | 6/333 | L |
| Efficacy (probably blinded rater) | COG TR | SMD=–0.20 (–0.40 to –0.01) | Mixed | 11/566 | L |
| Efficacy (most proximal rater) | COG TR  BT | SMD=–0.37 (–0.66 to –0.09)  SMD=–0.35 (–0.50 to –0.19) | Mixed  Mixed | 14/727  19/1,430 | L  L |
| Efficacy (teacher-rated) | ST | SMD=–0.26 (–0.52 to –0.01) | Mixed | 6/615 | L |
| Efficacy (parent-rated) | BT-Parental  ST | SMD=–0.65 (–1.05 to –0.25)  SMD=–0.56 (–0.74 to –0.38) | TAU/WL/LIP  Mixed | 8/399  10/934 | L  L |
| Aggressive behavior | BI | SMD=–0.40 (–0.71 to –0.10) | Mixed | 5/350 | L |
| Functioning: academic | ST  BT | SMD=–0.33 (–0.51 to –0.14)  SMD=–0.28 (–0.59 to –0.06) | Mixed  Mixed | 7/695  9/817 | L  L |
| Efficacy (most proximal rater) | Neurofeedback | SMD=–0.35 (–0.59 to –0.11) | Mixed | 13/540 | M |
| Efficacy (parent-rated) | Neurofeedback | SMD=–0.32 (p=0.013) | Mixed | 16/706 | L |
| Autism spectrum disorder | | | | | |
| Efficacy: socialization (mixed rater) | PCIT | SMD=–0.22 (–0.36 to –0.09) | Mixed | 13/846 | L |
| Efficacy: language (mixed rater) | PCIT | SMD=–0.16 (–0.31 to –0.02) | Mixed | 13/785 | L |
| Efficacy: language comprehension (parent-rated) | PCIT | SMD=–0.29 (–0.56 to –0.01) | Mixed | 3/204 | L |
| Anxiety (clinician-rated) | CBT | SMD=–1.05 (–1.65 to –0.45) | TAU/WL | 6/208 | L |
| Anxiety (parent-rated) | CBT | SMD=–1.00 (–1.80 to –0.21) | TAU/WL | 7/283 | L |
| Aggressive behavior | PCIT | SMD = –0.67 (–0.85 to –0.49) | Mixed | 9/521 | L |
| Functioning: shared/joint attention | ST-ToM  PCIT | SMD=-0.55 (-0.99 to -0.11)  SMD=–0.41 (–0.68 to –0.14) | TAU/WL  Mixed | 2/88  3/215 | L  L |
| Functioning: social skills | SST-Computer  SST  SST-Face to face | SMD=–0.93 (–1.29 to –0.57)  SMD=–0.83 (–1.07 to –0.60)  SMD=–0.81 (–1.08 to –0.53) | TAU/WL  TAU/WL  TAU/WL | 5/138  18/1,266  14/1,128 | L  L  L |
| Functioning: parent synchrony | PCIT | SMD=–0.90 (–1.23 to –0.56) | Mixed | 3/244 | L |
| Global illness severity | PCIT | SMD=–0.30 (–0.52 to –0.08) | Mixed | 6/316 | L |
| Irritability | PCIT | SMD=–0.59 (–0.88 to –0.30) | Mixed | 8/653 | L |
| Depressive disorders | | | | | |
| Efficacy (mixed rater) | CBT | SMD=–0.53 (–0.82 to –0.24) | Mixed | 11/809 | M |
| Oppositional defiant disorder (ODD) | | | | | |
| Efficacy (mixed rater) | BI | SMD=–0.79 (–0.93 to –0.64) | WL/AC | 17/NR | L |
| Tourette's syndrome | | | | | |
| Efficacy (clinician-rated) | BT | SMD=–0.64 (–0.99 to –0.29) | WL/LIP | 2/133 | L |
| Disruptive behavior/dissocial/conduct disorders (with or without ADHD) | | | | | |
| Efficacy: ADHD  symptoms (mixed rater) | BI | SMD=–0.34 (–0.64 to –0.05) | WL/AC | 11/518 | L |
| Efficacy: ADHD symptoms (parent-rated) | BI | SMD=–0.68 (–0.91 to –0.44) | WL/AC | 5/322 | L |
| Efficacy: externalizing (mixed rater) | BI | SMD=–0.52 (–0.68 to –0.36) | WL/AC | 10/881 | L |
| Efficacy: ODD  symptoms (mixed rater) | BI | SMD=–0.88 (–1.24 to –0.51) | WL/AC | 10/335 | L |
| Efficacy: ODD symptoms (parent-rated) | BI | SMD=–0.81 (–1.20 to –0.42) | WL/AC | 4/199 | L |
| Aggressive behavior | BI | SMD–=–0.28 (–0.46 to –0.10) | WL/AC | 18/794 | L |
| Cognition: attention | BI | SMD=–0.38 (–0.52 to –0.23) | WL/AC | 15/588 | L |
| Functioning | BI | SMD=–0.39 (–0.52 to –0.26) | WL/AC | 22/1,027 | L |

SMD – standardized mean difference, WL – waiting list, AC – active control, TAU – treatment as usual, LIP – low intensity psychosocial intervention, Q – quality (H – high, M – medium, L – low), BT – behavioral therapy, CBT – cognitive behavioral therapy, COG TR - cognitive training, BI – combination of parental and child behavioral interventions, ST – skills training, PCIT – parent-child interaction therapy, SST – social skills training, ST-ToM, skills training: precursors of Theory of Mind, NR – not reported. SMDs<0 indicate intervention is more effective than control.