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, to a smaller extent, behavioral therapy in attention-deficit/hyperactivity disorder; aripiprazole, risperidone and several psychosocial interventions in autism; risperidone and behavioral interventions in disruptive behavior disorders; several antipsychotics in schizophrenia spectrum disorders; fluoxetine, the combination of fluoxetine and cognitive behavioral therapy (CBT), and interpersonal therapy in depression; aripiprazole in mania; fluoxetine and group CBT in anxiety disorders; fluoxetine/selective serotonin reuptake inhibitors, CBT, and behavioral therapy with exposure and response prevention in obsessive-compulsive disorder; CBT in post-traumatic stress disorder; imipramine and alarm behavioral intervention in enuresis; behavioral therapy in encopresis; and family therapy in 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

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Many mental disorders have an onset with clinically relevant manifestations in childhood or adolescence, followed frequently by a chronic illness course into adulthood[1,2]. 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 disorders[3]. 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 disability[4]. 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 adults[9], most antidepressants have not been shown to be superior to placebo in children and adolescents with major depressive disorder[7,10]. Similarly, yet to a lower extent, antidepressants may not be as effective in children and adolescents with anxiety disorders as in adults[11].

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 depression[10] or anxiety[12]

disorders. Yet, when compared with placebo/sham interventions, most significant findings favoring psychosocial interventions vs. placebo disappear[10,12]. Effect sizes also vary according to design, blinding, patient selection (baseline severity) and choice of the control group[13] 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 disorders[14].

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-11[15], 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 disorder, 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 medications, psychosocial interventions, and brain stimulation techniques.

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, cognitive behavioral therapy (CBT), problem solving, dialectical behavioral therapy, family-based therapy, interpersonal psychotherapy, mentalization based therapy, psychodynamic psychotherapy, supportive therapy, social skills training, acceptance and commitment therapy, mindfulness, eye movement desensitization and reprocessing, narrative exposure therapy, cognitive remediation therapy, cognitive training, parent-child interaction therapy, 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 3[18]. 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 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 models[19]. 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 NMAs[5,20,21] and 21 MAs[22-42]; for autism, one NMA[43] and 21 MAs[12,44-63] (including one focusing on comorbid anxiety disorders and autism)[12]; for depressive disorders, two NMA[7,10] and seven MAs[64-70]; for obsessive-compulsive disorder, one NMA[71] and six MAs[72-77]; for anxiety disorders, two NMAs[11,78] and five MAs[12,79-82] (plus two MAs specific on social anxiety disorder[83,84]); for enuresis, one NMA[85] and six MAs[86-91], for disruptive behavior/dissocial/conduct disorders, five MAs[92-96] (plus one focusing on youth with comorbid ADHD)[25]; for eating disorders, one NMA[97] and four MAs[98-101]; for schizophrenia spectrum disorders, three NMAs[8,102,103] and two MAs[104,105]; for bipolar disorder, four MAs[106-109]; for tic disorder, two MAs[110,111]; for Tourette's disorder, two MAs[112,113]; for encopresis, two MAs[114,115]; for developmental coordination disorder, one MA[116]; and for PTSD, one MA[117].

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, fluoxe-

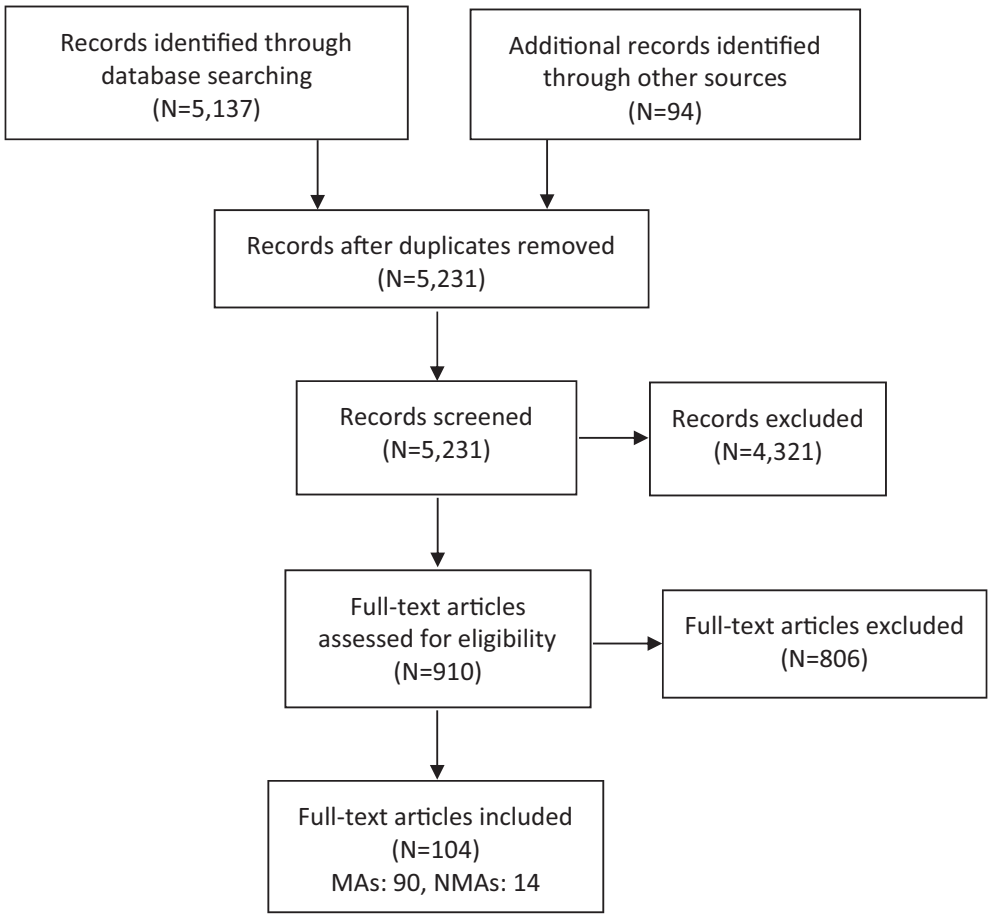

Figure 1 PRISMA flow chart, MAs – meta-analyses, NMAs – network meta-analyses

tine, guanfacine, lurasidone and quetiapine (7 outcomes), and asenapine, clonidine, olanzapine, paliperidone and sertraline (6 outcomes). Monotherapy psychosocial interventions most covered by the literature were CBT (12 outcomes), behavioral therapy (9 outcomes), parent-child interaction therapy (7 outcomes), and CBT-oriented, psychodynamic-oriented and family-based therapies (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 was 10 (IQR: 7-11), being low in 0.8%, moderate in 24.7%, and high in 74.4% of the NMAs/MAs, while the AMSTAR-Content median quality score was 4 (IQR: 3-5), being low in 30.1%, moderate in 58.6%, and high in 11.3%.

Across NMAs and MAs of RCTs of psychosocial interventions, the median AMSTAR quality score was 11 (IQR: 10-12), being low in none of the NMAs/MAs, moderate in 8.2%, and high in 91.8%, while the median AMSTAR-Content quality score was 2 (IQR: 1-3), being low in 87.4%, moderate in 12.6%, and high in none.

Across brain stimulation interventions, the median AMSTAR quality score was 9 (IQR: 8-10), being low in none of the NMAs/MAs, medium in 16.7%, and high in 83.3%, while the median AMSTAR-Content quality score was 2 (IQR: 1-4), being low in 66.7%, moderate in 33.3%, and high in none.

Efficacy, acceptability and tolerability of pharmacological, psychosocial, and brain stimulation interventions (Tables 2-7)

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.

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 al[79]	MA	115/7,719	AD	PBO	PE, REM	10	4
Dobson et al[11]	NMA	22/2,623	AD	PBO	RES, ACD, AED, S	7	5
Zhang et al[80]	MA	7/358	CB	WL/NT	PE	9	2
James et al[12]	MA	87/5,964	CB	PBO, WL/NT, TAU, PS	PE, REM, DEP, F, ACD	11	3
Zhou et al[78]	NMA	101/6,625	CB	PBO, WL/NT, TAU, PS	PE, QoL, ACD	11	2
Sigurvinsdóttir et al[81]	MA	81/5,913	CB	WL/NT, TAU, PS	REM	10	1
James et al[82]	MA	41/1,955	CB	TAU, PS	PE, REM	11	1.5
Anorexia nervosa							
Fisher et al[99]	MA	21/1,407	FB	TAU, PS	PE, ACD, REM	10	1
van den Berg et al[100]	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 al[83]	MA	17/1,134	CB	PBO, WL/NT	PE, REM, DEP, QoL, ACD	10	2
Kreuze et al[84]	MA	42/3,239	CB	PBO, TAU, LIP	AG, F	10	2.5
Attention-deficit/hyperactivity disorder (ADHD)							
Cortese et al[5]	NMA	133/18,199	AD, STIM, α2	PBO, AD, STIM	PE, AED, GLO	11	9
Otasowie et al[22]	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 al[34]	MA	28/4,699	AD	PBO	PE	8	2
Luan et al[21]	NMA	73/15,025	AD, STIM, α2	PBO, PHARMA	PE, AED, ID	7	4
Catalá-López et al[20]	NMA	190/26,114	AP, AD, STIM, α2, CB, CT, NF, COMB	PBO	RES, ACD, GLO	10	4
Schachter et al[36]	MA	62/2,897	STIM	PBO	AG	9	1
Schwartz et al[37]	MA	25/3,928	AD, STIM	PBO	AG, F, QoL, S	7	5
Coghill et al[38]	MA	60/1,993	STIM	PBO	COG	8	2
Storebø et al[39]	MA	185/12,245	STIM	PBO	QoL	8	5
Bangs et al[40]	MA	32/7,248	AD, STIM	PBO	S	3	4
Hirota et al[41]	MA	12/2,276	α2+	PBO	PE, ACD, AED, ID	6	3.5
Storebø et al[42]	MA	25/2,690	SKILL, COMB	WL/NT	PE, COG, F	11	2
Sun et al[24]	MA	8/423	STIM	PBO	PE, ACD, AED	11	2
Battagliese et al[25]	MA	24/1,690	BT	MIX	PE, AG, COG, F	7	1
Faraone et al[26]	MA	4/216	STIM	STIM	AG	2	3
Van Doren et al[27]	MA	10/506	NF	PHARMA, PS	PE, RES, ACD	8	2
Cortese et al[28]	MA	16/759	CT	MIX	PE, COG	11	1
Daley et al[29]	MA	32/2,077	BT	MIX	PE, COG	9	2
Bikic et al[30]	MA	12/1,054	SKILL	MIX	PE, COG	8	2
Mulqueen et al[31]	MA	8/399	BT	MIX	PE	6	1
Cortese et al[32]	MA	13/520	NF	MIX	PE, COG	9	1.5
Bussalb et al[33]	MA	16/706	NF	MIX	PE	4	2
Faraone et al[35]	MA	7/384	STIM	PBO	AG	2	2

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 *(continued)*

	Source	Number of RCTs/ patients	Intervention	Controls	Outcomes	A	C
Autism spectrum disorder							
Maneeton et al[44]	MA	3/408	AP	PBO	PE, RES, GLO	7	4
Maneeton et al[52]	MA	7/372	AP	PBO	REL, RES	7	3.5
Zhou et al[53]	MA	64/3,499	STIM	PBO	PP	9	3
Murza et al[54]	MA	16/837	SKILL	WL/NT	F	8	0.5
Fletcher-Watson et al[56]	MA	22/695	SKILL	WL/NT, TAU	F	10	1
Sturman et al[55]	MA	4/113	STIM	PBO	PE	10	1
Cohen et al[57]	MA	15/995	AP	PBO	RES	5	1
Hirota et al[58]	MA	7/171	MS	PBO	RES, AG, ACD, AED, ID	6	4
Fallah et al[43]	NMA	8/878	AP	PBO, AP	AG	7	1
D'Alò et al[59]	MA	15/1,124	AP	PBO	ACD, AED	9	5
Ospina et al[60]	MA	69/2,585	BT	WL/NT, PS	PE	9	1
Reichow et al[61]	MA	5/196	SKILL	WL/NT	PE	10	1
James et al[12]	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 al[63]	MA	19/1,205	PCI	TAU/LIP, MIX	PE, COG	5	1
Yu et al[45]	MA	14/555	BT	TAU	PE, F	9	0
Oono et al[46]	MA	17/919	PCI	MIX	PE, F, GLO	10	1
Parsons et al[47]	MA	21/925	SKILL	MIX	PE	9	1
Kreslins et al[48]	MA	10/470	CB	MIX	ANX	9	0
Tarver et al[49]	MA	9/521	PCI	MIX	AG	8	2
Soares et al[50]	MA	18/1,266	SKILL	MIX	F	8	2
Postorino et al[51]	MA	8/653	PCI	MIX	IR	8	1
Bipolar disorder, depressive episode							
Maneeton et al[106]	MA	3/251	AP	PBO	PE, RES, REM, GLO, ACD, AED	9	3
Bipolar disorder, manic episode							
Meduri et al[107]	MA	22/5,437	AP	PBO	PE, RES, ACD, AED, ID	10	5
Liu et al[108]	MA	46/2,666	MS	PBO	RES	7	6
Jochim et al[109]	MA	25/3,252	MS, AP	PBO, MS	ACD	10	4
Bulimia nervosa							
Linardon et al[101]	MA	79/NR	CB	PS	PE	6	0
Depressive disorders							
Zhou et al[10]	NMA	71/9,510	AD, PSD-O, FB, CB, COMB	PBO, WL/NT, TAU/LIP, PHARMA, PS	PE, ACD, S	11	5
Cipriani et al[7]	NMA	34/5,260	AD	PBO, PHARMA	RES, AED	11	5
Spielmans & Gerwig[64]	MA	8/1,756	AD	PBO	QoL	5	5
Kato et al[65]	MA	40/8,890	AD	PBO	REL	9	3
Whittington et al[66]	MA	2/376	AD	PBO	REM	9	2.5
Watanabe et al[67]	MA	27/1,744	PSD-O	WL/PBO	RES	7	2
Cox et al[68]	MA	9/882	AD, CB, COMB	PHARMA, PS	REM, S	10	3

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 *(continued)*

	Source	Number of RCTs/ patients	Intervention	Controls	Outcomes	A	C
Dubicka et al[69]	MA	5/1,206	COMB	PHARMA, PS	RES, F, S	7	3
Klein et al[70]	MA	11/809	CB	MIX	PE	8	4
Disruptive behavior/dissocial/conduct disorders							
Seida et al[92]	MA	62/NR	AP	PBO	PE, AG, GLO	9	3.5
Loy et al[93]	MA	10/896	AP	PBO	PE, AG	10	4
Pringsheim et al[94]	MA	18/1,195	MS	PBO	AG	10	2
Ipser & Stein[95]	MA	14/823	PHARMA	PBO	AG, ACD, GLO, RES	6	1.5
Battagliese et al[25]	MA	24/1,690	CB	WL/NT, MIX	PE	7	1.5
McQuire et al[96]	MA	14/912	AP, MS	PBO	AG	8	2
Developmental coordination disorder							
Miyahara et al[116]	MA	15/649	SKILL	WL/NT	PE	10	1
Eating disorders							
Couturier et al[98]	MA	6/369	FB	PS	REM	8	3
Encopresis							
Freeman et al[114]	MA	10/562	COMB	TAU	PE, RES	7	1
Brazzelli et al[115]	MA	21/1,371	COMB	TAU	RES	10	1
Enuresis							
Caldwell et al[86]	MA	74/5,983	BT, COMB	PHARMA, PS, WL/NT	PE, RES	11	1
Caldwell et al[87]	MA	64/4,071	AD, COMB	PBO, PHARMA, PS	PE, RES	11	1
Caldwell et al[88]	MA	16/1,643	BT	PS, WL/NT	RES	10	1
Buckley et al[89]	MA	27/1,803	SKILL, COMB	TAU, PHARMA	REM	10	1
Deshpande et al[90]	MA	40/2,440	AD, COMB	PHARMA	RES, REL	10	1
Peng et al[91]	MA	15/1,502	PHARMA	PS	ACD	9	4
Song et al[85]	NMA	18/1,649	PHARMA, COMB	PHARMA, PS	RES, REL	9	4
Obsessive-compulsive disorder							
Skapinakis et al[71]	NMA	86/15,585	AD, CB, COMB	PBO, WL/NT, PHARMA, PS	PE, ACD	10	3
Maneeton et al[72]	MA	3/188	AD	PBO	RES, GLO	9	2
McGuire et al[73]	MA	20/1,296	AD, CB	PBO, TAU/LIP, WL/NT	RES, REM	8	1
Locher et al[74]	MA	36/6,778	AD	PBO	AED	10	4
Geller[75]	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 al[117]	MA	14/758	CB	WL/NT, TAU/LIP	PE, RES, ANX, DEP, ACD	10	1
Schizophrenia spectrum disorders							
Krause et al[102]	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 al[8]	NMA	12/2,158	AP	PBO, PHARMA	GLO	8	3

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 *(continued)*

	Source	Number of RCTs/ patients	Intervention	Controls	Outcomes	A	C
Sarkar & Grover[104]	MA	15/995	AP	PHARMA	PE	5	1
Kumar et al[105]	MA	13/1,112	AP	PHARMA	AED	8	1
Tic disorder							
Bloch et al[110]	MA	9/477	STIM, AD	PBO	PE	4	1
Yu et al[111]	MA	15/1,070	MS	PHARMA	RES	7	3
Tourette's disorder							
Hollis et al[112]	MA	40/2,422	AP, α2, STIM, BT	PBO, MIX	PE	8	1
Zheng et al[113]	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

Focusing on the two best interventions, amphetamines had the highest 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 (see Table 2). 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).

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	**SMD=–1.02 (–1.19 to –0.85)**	PBO/Sham	46/9,926	H
	Methylphenidate	**SMD=–0.78 (–0.93 to –0.62)**	PBO/Sham	46/9,926	H
	Clonidine	**SMD=–0.71 (–1.17 to –0.24)**	PBO/Sham	46/9,926	H
	Guanfacine	**SMD=–0.67 (–0.85 to –0.50)**	PBO/Sham	46/9,926	H
	Modafinil	**SMD=–0.62 (–0.84 to –0.41)**	PBO/Sham	46/9,926	H
	Atomoxetine	**SMD=–0.56 (–0.66 to –0.45)**	PBO/Sham	46/9,926	H
Efficacy (teacher-rated)	Desipramine	**SMD=–0.97 (–1.66 to –0.28)**	PBO/Sham	2/89	L
	Methylphenidate	**SMD=–0.82 (–1.16 to –0.48)**	PBO/Sham	16/1,843	H
	Modafinil	**SMD=–0.76 (–1.15 to –0.37)**	PBO/Sham	16/1,843	H
	Amphetamines	**SMD=–0.55 (–0.83 to –0.27)**	PBO/Sham	5/745	M
	Guanfacine	SMD=–0.63 (–1.62 to 0.35)	PBO/Sham	16/1,843	H
	Atomoxetine	SMD=–0.32 (–0.82 to 0.18)	PBO/Sham	16/1,843	H
Efficacy (parent-rated)	Desipramine	**SMD=–1.42 (–1.99 to –0.85)**	PBO/Sham	2/99	L
	Amphetamines	**SMD=–1.07 (–1.36 to –0.79)**	PBO/Sham	23/3,796	H
	Methylphenidate	**SMD=–0.84 (–0.95 to –0.72)**	PBO/Sham	23/3,796	H
	Atomoxetine	**SMD=–0.60 (–0.71 to –0.50)**	PBO/Sham	23/3,796	H
	Modafinil	**SMD=–0.46 (–0.61 to –0.31)**	PBO/Sham	23/3,796	H
	Bupropion	SMD=–0.32 (–0.69 to 0.05)	PBO/Sham	2/124	L
	Guanfacine	SMD=–0.23 (–0.90 to 0.45)	PBO/Sham	23/3,796	H
Efficacy (mixed-rated)	Atomoxetine	**SMD=–0.17 (–0.23 to –0.11)**	PBO/Sham	36/7,579	M
	Amphetamines	**SMD=–0.18 (–0.28 to –0.09)**	PBO/Sham	36/7,579	M
	Methylphenidate	**SMD=–0.14 (–0.21 to –0.08)**	PBO/Sham	36/7,579	M
	Guanfacine	**SMD=–0.16 (–0.26 to –0.05)**	PBO/Sham	36/7,579	M
	Clonidine	SMD=–0.10 (–0.23 to 0.03)	PBO/Sham	36/7,579	M
Response	Desipramine	**OR=36.76 (9.17-214)**	PBO/Sham	113/19,398	M
	Amphetamines	**OR=7.45 (5.1-11.09)**	PBO/Sham	113/19,398	M
	Modafinil	**OR=5.51 (3.04-10.32)**	PBO/Sham	113/19,398	M
	Methylphenidate	**OR=5.26 (4.09-6.82)**	PBO/Sham	113/19,398	M
	Clonidine	**OR=3.96 (1.89-8.41)**	PBO/Sham	113/19,398	M
	Atomoxetine	**OR=3.63 (2.81-4.73)**	PBO/Sham	113/19,398	M
	Guanfacine	**OR=3.29 (2.27-4.82)**	PBO/Sham	113/19,398	M
Aggressive behavior	Amphetamines	**SMD=–1.15 (–1.38 to –0.93)**	PBO/Sham	3/84	L
	Methylphenidate	SMD=–0.26 (–1.10 to 0.68)	PBO/Sham	2/181	L
	Atomoxetine	RR=1.34 (0.91 to 1.97)	PBO/Sham	15/2,067	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

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 *(continued)*

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/patients	Q
Acceptability	Clonidine	**OR=0.40 (0.20-0.78)**	PBO/Sham	171/22,961	M
	Methylphenidate	**OR=0.59 (0.46-0.75)**	PBO/Sham	171/22,961	M
	Aripiprazole	OR=0.61 (0.02-25.34)	PBO/Sham	171/22,961	M
	Modafinil	OR=0.67 (0.37-1.24)	PBO/Sham	171/22,961	M
	Desipramine	OR=0.70 (0.17-2.89)	PBO/Sham	171/22,961	M
	Amphetamines	OR=0.78 (0.52-1.18)	PBO/Sham	171/22,961	M
	Guanfacine	OR=0.79 (0.54-1.14)	PBO/Sham	171/22,961	M
	Atomoxetine	OR=0.85 (0.68-1.07)	PBO/Sham	171/22,961	M
	Bupropion	OR=1.54 (0.39-6.76)	PBO/Sham	171/22,961	M
Tolerability	Methylphenidate	OR=1.31 (0.79-2.25)	PBO/Sham	60/12,188	M
	Modafinil	OR=1.34 (0.57-3.18)	PBO/Sham	60/12,188	M
	Amphetamines	OR=1.38 (0.64-3.00)	PBO/Sham	60/12,188	M
	Clonidine	OR=2.32 (0.63-8.94)	PBO/Sham	58/NR	H
	Bupropion	OR=3.60 (0.34-130)	PBO/Sham	60/12,188	M
	Atomoxetine	**OR=1.48 (1.01-2.18)**	PBO/Sham	60/12,188	M
	Guanfacine	**OR=3.39 (1.93-6.3)**	PBO/Sham	60/12,188	M
Discontinuation due to inefficacy	Amphetamine	**OR=0.11 (0.05-0.20)**	PBO/Sham	45/9,087	M
	Clonidine	**OR=0.29 (0.13-0.56)**	PBO/Sham	45/9,087	M
	Methylphenidate	**OR=0.31 (0.18-0.53)**	PBO/Sham	45/9,087	M
	Guanfacine	**OR=0.37 (0.26-0.54)**	PBO/Sham	45/9,087	M
	Atomoxetine	**OR=0.47 (0.33-0.67)**	PBO/Sham	45/9,087	M
	Bupropion	OR=1.97 (0.19-57.4)	PBO/Sham	45/9,087	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	**OR=7.71 (5.52-10.77)**	PBO/Sham	40/NR	H
	Atomoxetine	**OR=2.28 (1.38-3.76)**	PBO/Sham	40/NR	H
	Guanfacine	**OR=3.63 (2.36-5.57)**	PBO/Sham	40/NR	H
	Methylphenidate	**OR=5.57 (3.99-7.79)**	PBO/Sham	40/NR	H
	Modafinil	**OR=3.22 (1.91-5.43)**	PBO/Sham	40/NR	H
	Clonidine	OR=2.78 (0.91-8.53)	PBO/Sham	40/NR	H
Global illness severity	Amphetamines	**SMD=–0.86 (–1.72 to –0.01)**	PBO/Sham	2/86	M
	Desipramine	**OR=26.41 (7.41-94.18)**	PBO/Sham	2/103	L
Quality of life	Methylphenidate	**SMD=–0.61 (–0.80 to –0.42)**	PBO/Sham	3/514	M
	Atomoxetine	**SMD=–0.39 (–0.50 to –0.28)**	PBO/Sham	16/2,361	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

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 *(continued)*

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/patients	Q
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	**OR=2.97 (1.53-5.88)**	PBO/Sham	113/19,398	M
	Cognitive training	OR=0.70 (0.12-3.87)	PBO/Sham	113/19,398	M
Acceptability	Behavioral therapy	**OR=0.58 (0.33-0.99)**	PBO/Sham	171/22,961	M
	Cognitive training	OR=1.32 (0.71-2.52)	PBO/Sham	171/22,961	M
Functioning: academic	Social skills training	SMD=–0.15 (–0.31 to 0.01)	WL/NT	5/642	M
Global illness severity	Behavioral therapy	**OR=2.99 (1.21-7.31)**	PBO/Sham	113/19,398	M
	Cognitive training	OR=0.39 (0.01-5.80)	PBO/Sham	113/19,398	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	**SMD=–0.43 (–0.70 to –0.15)**	WL/NT	4/337	L
	Social skills training	**SMD=–0.19 (–0.32 to –0.06)**	WL/NT	15/1,609	M
Functioning: social skills (teacher-rated)	Social skills training + parental involvement	SMD=–0.15 (–0.41 to 0.12)	WL/NT	4/632	M
	Social skills training	SMD=–0.11 (–0.22 to 0.00)	WL/NT	11/1,271	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	**OR=55.63 (3.18-29.52x10^2)**	PBO/Sham	113/19,398	M
	Methylphenidate + clonidine	**OR=21.91 (5.52-105.40)**	PBO/Sham	113/19,398	M
	Atomoxetine + parent training	**OR=2.48 (0.51-11.79)**	PBO/Sham	113/19,398	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	**SMD=–0.32 (–0.53 to–0.12)**	PBO/Sham	3/400	M
	Methylphenidate	SMD=–0.18 (–0.46 to 0.11)	PBO/Sham	5/127	M
	Atomoxetine	SMD=–0.16 (–0.50 to 0.18)	PBO/Sham	4/281	L

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 *(continued)*

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/patients	Q
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	**OR=2.57 (1.35-4.86)**	PBO/Sham	3/241	L
	Aripiprazole	**RR=2.08 (1.24-3.46)**	PBO/Sham	3/400	L
Aggressive behavior	Risperidone	**SMD=–0.29 (–0.48 to –0.11)**	PBO/Sham	8/878	L
	Aripiprazole	**SMD=–0.24 (–0.40 to –0.08)**	PBO/Sham	8/878	L
	Valproate	SMD=–0.18 (–0.71 to 0.35)	PBO/Sham	2/57	M
	Lurasidone	SMD=–0.05 (–0.27 to 0.18)	PBO/Sham	8/878	L
Acceptability	Risperidone	**RR=0.52 (0.32-0.86)**	PBO/sham	6/379	M
	Antipsychotics	**RR=0.61 (0.48-0.78)**	PBO/Sham	15/1,124	M
	Aripiprazole	**RR=0.67 (0.49-0.90)**	PBO/Sham	5/526	M
	Haloperidol	RR=0.80 (0.24-2.62)	PBO/Sham	2/60	M
	Mood stabilizers	RR=1.27 (0.53-3.06)	PBO/Sham	5/125	M
Tolerability	Risperidone	RR=0.71 (0.17-2.92)	PBO/Sham	5/339	M
	Antipsychotics	RR=0.99 (0.55-1.79)	PBO/Sham	12/1,010	M
	Mood stabilizers	RR=1.13 (0.36-3.53)	PBO/Sham	4/112	M
	Aripiprazole	RR=1.24 (0.57-2.71)	PBO/Sham	4/493	M
Discontinuation due to inefficacy	Mood stabilizers	RR=2.11 (0.36-12.42)	PBO/Sham	3/60	M
Global illness severity	Aripiprazole	**SMD=–0.54 (–0.77 to –0.32)**	PBO/Sham	3/400	M
	Risperidone	**OR=10.5 (4.80-22.60)**	PBO/Sham	6/446	L
	Mood stabilizers	RR=1.55 (0.39-6.21)	PBO/Sham	3/77	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	SMD=–0.53 (–1.12 to 0.05)	WL/NT	2/48	L
	Social skills training	SMD=–0.34 (–0.88 to 0.20)	WL/NT	2/54	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	**OR=15.6 (1.91-128.1)**	PBO/Sham	2/47	L
	Lithium	**RR=4.56 (1.97-10.56)**	PBO/Sham	3/116	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

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 *(continued)*

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/patients	Q
Aggressive behavior (mixed-rated)	Risperidone	**SMD=–0.60 (–0.89 to –0.31)**	PBO/Sham	2/188	L
	Mixed (risperidone, lithium, methylphenidate)	SMD=–1.93 (–3.88 to 0.02)	PBO/Sham	4/172	L
Acceptability	Mixed (risperidone, lithium, methylphenidate)	RR=0.97 (0.60-1.55)	PBO/Sham	8/631	L
Global illness severity	Risperidone	**SMD=–1.31 (–1.88 to –0.74)**	PBO/Sham	2/58	L
	Mixed (risperidone, quetiapine)	**SMD=–0.30 (–0.49 to –0.12)**	PBO/Sham	5/435	M
	Mixed (carbamazepine, lithium, amphetamines)	**RR=2.39 (1.10-5.21)**	PBO/Sham	4/136	L
Psychosocial interventions					
Efficacy (parent-rated)	Parental + child behavioral interventions	**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	**SMD=–1.09 (–1.39 to –0.79)**	PBO/Sham	4/257	L
	Aripiprazole	**SMD=–0.64 (–0.91 to –0.36)**	PBO/Sham	2/308	L
	Valproate	SMD=–0.06 (–0.75 to 0.63)	PBO/Sham	2/57	L
Aggressive behavior (mixed-rated)	Risperidone	**SMD=–0.70 (–1.01 to –0.39)**	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	SMD=–0.44 (–0.91 to 0.02)	PBO/Sham	2/75	L
	Methylphenidate	SMD=–0.28 (–0.58 to 0.03)	PBO/Sham	4/191	L
Tourette's disorder					
Efficacy (clinician-rated)	Antipsychotics (haloperidol, pimozide, risperidone, ziprasidone)	**SMD=–0.74 (–1.08 to –0.41)**	PBO/Sham	4/75	L
	Guanfacine	**SMD=–0.73 (–1.26 to –0.20)**	PBO/Sham	2/58	L
	Methylphenidate	SMD=–0.17 (–0.46 to 0.11)	PBO/Sham	4/161	L

RCTs – randomized controlled trials, SMD – standardized mean difference, OR – odds ratio, RR – risk ratio, PBO – placebo, WL – waiting list, NT – no treatment, NR – not reported, Q – quality (H – high, M – medium, L – low). Bold prints indicate significant values. SMDs<0 indicate that 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.

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 (see Table 2). 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 Tables 3 and 5).

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 3 and 6). 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 (see Table 3), and CBT plus SSRI was 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 waiting list on the primary efficacy outcome (small effect size) and response (large effect size), 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).

Among monotherapy psychosocial interventions, CBT was 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) and functioning (large effect size), and also to placebo concerning remission (small effect size) (see Table 4). Behavioral therapy with exposure and response prevention outperformed TAU for both response and acceptability (small effect size) (see 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 Tables 4, 5 and 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).

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	**SMD=–0.74 (–1.05 to –0.44)**	PBO/Sham	28/3,003	L
	Risperidone	**SMD=–0.62 (–0.89 to –0.34)**	PBO/Sham	28/3,003	L
	Lurasidone	**SMD=–0.48 (–0.71 to –0.25)**	PBO/Sham	28/3,003	M
	Aripiprazole	**SMD=–0.43 (–0.63 to –0.24)**	PBO/Sham	28/3,003	M
	Quetiapine	**SMD=–0.42 (–0.65 to –0.19)**	PBO/Sham	28/3,003	M
	Paliperidone	**SMD=–0.42 (–0.66 to –0.18)**	PBO/Sham	28/3,003	L
	Asenapine	**SMD=–0.38 (–0.66 to –0.11)**	PBO/Sham	28/3,003	M
	Ziprasidone	SMD=–0.14 (–0.40 to 0.11)	PBO/Sham	28/3,003	L
Response	Risperidone	**OR=3.46 (1.92-6.23)**	PBO/Sham	28/3,003	L
	Olanzapine	**OR=2.64 (1.07-4.18)**	PBO/Sham	28/3,003	L
	Lurasidone	**OR=2.56 (1.45-4.48)**	PBO/Sham	28/3,003	M
	Paliperidone	**OR=2.12 (1.07-4.18)**	PBO/Sham	28/3,003	L
	Quetiapine	**OR=1.86 (1.03-3.32)**	PBO/Sham	28/3,003	M
	Asenapine	OR=1.73 (0.96-3.10)	PBO/Sham	28/3,003	M
Global illness severity	Olanzapine	**SMD=–0.6 (–1.18 to –0.02)**	PBO/Sham	13/2,210	M
	Risperidone	**SMD=–0.50 (–0.73 to –0.27)**	PBO/Sham	12/2,158	L
	Paliperidone	**SMD=–0.44 (–0.67 to –0.22)**	PBO/Sham	12/2,158	L
	Lurasidone	**SMD=–0.41 (–0.77 to –0.05)**	PBO/Sham	13/2,210	M
	Quetiapine	**SMD=–0.41 (–0.77 to –0.05)**	PBO/Sham	13/2,210	M
	Ziprasidone	**SMD=–0.40 (–0.68 to –0.12)**	PBO/Sham	13/2,210	M
	Aripiprazole	**SMD=–0.35 (–0.59 to –0.11)**	PBO/Sham	13/2,210	M
	Asenapine	**SMD=–0.29 (–0.53 to –0.06)**	PBO/Sham	13/2,210	M
Acceptability	Paliperidone	**OR=0.26 (0.08-0.80)**	PBO/Sham	28/3,003	L
	Risperidone	**OR=0.31 (0.14-0.72)**	PBO/Sham	28/3,003	L
	Olanzapine	**OR=0.36 (0.15-0.85)**	PBO/Sham	28/3,003	L
	Lurasidone	OR=0.53 (0.18-1.55)	PBO/Sham	28/3,003	M
	Ziprasidone	OR=0.59 (0.22-1.58)	PBO/Sham	28/3,003	L
	Quetiapine	OR=0.63 (0.27-1.43)	PBO/Sham	28/3,003	M
	Asenapine	OR=0.91 (0.33-2.56)	PBO/Sham	28/3,003	M
	Aripiprazole	OR=1.48 (0.60-3.67)	PBO/Sham	28/3,003	M

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 *(continued)*

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/ patients	Q
Tolerability	Lurasidone	OR=0.45 (0.16-1.22)	PBO/Sham	13/2,210	M
	Ziprasidone	OR=0.99 (0.45-2.30)	PBO/Sham	13/2,210	M
	Risperidone	OR=2.38 (0.57-13.56)	PBO/Sham	13/2,210	M
	Aripiprazole	OR=2.54 (0.70-14.48)	PBO/Sham	13/2,210	M
	Asenapine	OR=2.67 (0.82-12.47)	PBO/Sham	13/2,210	M
	Quetiapine	OR=3.29 (0.92-16.75)	PBO/Sham	13/2,210	M
	Olanzapine	**OR=7.76 (1.23-87.44)**	PBO/Sham	13/2,210	M
	Paliperidone	**OR=23.12 (2.38-778.70)**	PBO/Sham	13/2,210	M
Discontinuation due to inefficacy	Paliperidone	**OR=0.10 (0.04-0.28)**	PBO/Sham	28/3,003	L
	Olanzapine	**OR=0.14 (0.06-0.31)**	PBO/Sham	28/3,003	L
	Risperidone	**OR=0.17 (0.07-0.42)**	PBO/Sham	28/3,003	L
	Ziprasidone	**OR=0.41 (0.20-0.84)**	PBO/Sham	28/3,003	L
	Lurasidone	OR=0.39 (0.09-1.77)	PBO/Sham	28/3,003	M
	Asenapine	OR=0.63 (0.23-1.73)	PBO/Sham	28/3,003	M
Depressive disorders					
Pharmacological interventions					
Efficacy (clinician-rated)	Fluoxetine	**SMD=–0.51 (–0.84 to –0.18)**	PBO/Sham	70/8,906	M
	Desipramine	SMD=–0.43 (–1.26 to 0.39)	PBO/Sham	70/8,906	M
	Duloxetine	SMD = –0.22 (–0.85 to 0.42)	PBO/Sham	70/8,906	M
	Venlafaxine	SMD = –0.25 (–0.87 to 0.36)	PBO/Sham	70/8,906	M
	Mirtazapine	SMD = –0.23 (–0.97 to 0.51)	PBO/Sham	70/8,906	M
	Citalopram	SMD=–0.18 (–0.89 to 0.55)	PBO/Sham	70/8,906	M
	Escitalopram	SMD=–0.17 (–0.88 to 0.54)	PBO/Sham	70/8,906	M
	Paroxetine	SMD=–0.16 (–0.67 to 0.35)	PBO/Sham	70/8,906	M
	Nefazodone	SMD=–0.14 (–0.85 to 0.57)	PBO/Sham	70/8,906	M
	Desvenlafaxine	SMD=–0.12 (–0.79 to 0.54)	PBO/Sham	70/8,906	M
	Sertraline	SMD=–0.11 (–0.71 to 0.49)	PBO/Sham	70/8,906	M
	Imipramine	SMD=–0.03 (–0.75 to 0.68)	PBO/Sham	70/8,906	M
	Vilazodone	SMD=–0.09 (–1.09 to 0.90)	PBO/Sham	70/8,906	M
	Amitriptyline	SMD=0.08 (–1.11 to 1.27)	PBO/Sham	70/8,906	M
	Nortriptyline	**SMD= 1.14 (0.46-1.81)**	PBO/Sham	70/8,906	M
Response	Nefazodone	**OR=2.1 (1.06-4.89)**	PBO/Sham	34/5,260	M
	Duloxetine	**OR=1.74 (1.12-2.84)**	PBO/Sham	34/5,260	M
	Fluoxetine	**OR=1.70 (1.25-2.39)**	PBO/Sham	34/5,260	M
	Desipramine	OR=1.59 (0.67-4.84)	PBO/Sham	34/5,260	M
	Escitalopram	OR=1.53 (0.96-2.58)	PBO/Sham	34/5,260	M
	Sertraline	OR=1.44 (0.79-2.97)	PBO/Sham	34/5,260	M
	Paroxetine	OR=1.3 (0.89-1.99)	PBO/Sham	34/5,260	M
	Venlafaxine	OR=1.16 (0.72-2.03)	PBO/Sham	34/5,260	M
	Citalopram	OR=1.02 (0.62-1.82)	PBO/Sham	34/5,260	M
	Imipramine	OR=0.83 (0.48-1.54)	PBO/Sham	34/5,260	M
	Nortriptyline	OR=0.57 (0.24-1.64)	PBO/Sham	34/5,260	M
	Amitriptyline	OR=0.22 (0.05-2.78)	PBO/Sham	34/5,260	M

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 *(continued)*

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/ patients	Q
Acceptability	Nefazodone	OR=0.49 (0.21-1.39)	PBO/Sham	66/9,075	M
	Vilazodone	OR=0.59 (0.27-1.54)	PBO/Sham	66/9,075	M
	Nortriptyline	OR=0.76 (0.28-3.41)	PBO/Sham	66/9,075	M
	Fluoxetine	OR=0.78 (0.56-1.15)	PBO/Sham	66/9,075	M
	Mirtazapine	OR=0.83 (0.40-2.08)	PBO/Sham	66/9,075	M
	Desvenlafaxine	OR=0.85 (0.47-1.74)	PBO/Sham	66/9,075	M
	Citalopram	OR=0.96 (0.52-1.97)	PBO/Sham	66/9,075	M
	Duloxetine	OR=1.04 (0.62-1.96)	PBO/Sham	66/9,075	M
	Venlafaxine	OR=1.12 (0.53-2.70)	PBO/Sham	66/9,075	M
	Amitriptyline	OR=1.16 (0.29-12.13)	PBO/Sham	66/9,075	M
	Paroxetine	OR=1.3 (0.81-2.27)	PBO/Sham	66/9,075	M
	Escitalopram	OR=1.4 (0.77-2.86)	PBO/Sham	66/9,075	M
	Sertraline	OR=162 (0.83-3.22)	PBO/Sham	66/9,075	M
	Desipramine	OR=2.21 (0.88-7.67)	PBO/Sham	66/9,075	M
	Imipramine	**OR=2.51 (1.26-6.25)**	PBO/Sham	66/9,075	M
Tolerability	Amitriptyline	OR=0.10 (0.02-32.16)	PBO/Sham	34/5,260	M
	Fluoxetine	OR=1.03 (0.5-2.7)	PBO/Sham	34/5,260	M
	Citalopram	OR=1.13 (0.45-3.66)	PBO/Sham	34/5,260	M
	Nefazodone	OR=1.29 (0.3-21.89)	PBO/Sham	34/5,260	M
	Mirtazapine	OR=1.36 (0.41-10.99)	PBO/Sham	34/5,260	M
	Paroxetine	OR=1.59 (0.77-3.95)	PBO/Sham	34/5,260	M
	Escitalopram	OR=1.64 (0.46-13.49)	PBO/Sham	34/5,260	M
	Desipramine	OR=2.85 (0.83-21.8)	PBO/Sham	34/5,260	M
	Sertraline	OR=2.94 (0.94-17.19)	PBO/Sham	34/5,260	M
	Duloxetine	**OR=2.80 (1.20-9.42)**	PBO/Sham	34/5,260	M
	Venlafaxine	**OR=3.19 (1.01-18.7)**	PBO/Sham	34/5,260	M
	Imipramine	**OR=5.49 (1.96-20.86)**	PBO/Sham	34/5,260	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	**RR=1.82 (1.25-2.63)**	PBO/Sham	2/315	M
	Sertraline	RR=1.09 (0.72-1.61)	PBO/Sham	2/376	M
Suicide attempt/ideation	Nefazodone	OR=0.29 (0.06-6.31)	PBO/Sham	34/NR	M
	Mirtazapine	OR=0.53 (0.10-40.83)	PBO/Sham	34/NR	M
	Imipramine	OR=0.59 (0.19-3.07)	PBO/Sham	34/NR	M
	Desvenlafaxine	OR=0.74 (0.41-1.49)	PBO/Sham	34/NR	M
	Escitalopram	OR=0.94 (0.44-2.55)	PBO/Sham	34/NR	M
	Duloxetine	OR=0.93 (0.55-1.71)	PBO/Sham	34/NR	M
	Fluoxetine	OR=1.11 (0.74-1.75)	PBO/Sham	34/NR	M
	Paroxetine	OR=1.71 (0.81-5.05)	PBO/Sham	34/NR	M
	Citalopram	OR=1.18 (0.46-4.43)	PBO/Sham	34/NR	M
	Vilazodone	OR=1.96 (0.45-100.00)	PBO/Sham	34/NR	M
	Sertraline	OR=2.22 (0.75-12.5)	PBO/Sham	34/NR	M
	Venlafaxine	**OR=8.33 (1.92-NC)**	PBO/Sham	34/NR	M

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 *(continued)*

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/ patients	Q
Psychosocial interventions					
Efficacy (clinician-rated)	IPT	**SMD=–1.37 (–2.04 to –0.7)**	WL/NT	70/8,906	L
	PSOLV	**SMD=–1.26 (–2.48 to –0.03)**	WL/NT	70/8,906	L
	FT	**SMD=–1.03 (–1.66 to –0.4)**	WL/NT	70/8,906	L
	CBT	**SMD=–0.94 (–1.40 to –0.48)**	WL/NT	70/8,906	L
	IPT	**SMD=–0.70 (–1.29 to –0.12)**	PBO/Sham	70/8,906	L
	FT	SMD=–0.36 (–0.95 to 0.24)	PBO/Sham	70/8,906	L
	CBT	SMD=–0.27 (–0.72 to 0.18)	PBO/Sham	70/8,906	L
	PSD-O	SMD=0.08 (–0.67 to 0.84)	PBO/Sham	70/8,906	L
Response	PSD-O	**RR=1.68 (1.08-2.63)**	WL/PBO/ Sham	2/83	L
Acceptability	IPT	OR=0.53 (0.20-1.15)	PBO/Sham	66/9,075	M
	IPT	OR=0.65 (0.19-1.62)	WL/NT	66/9,075	M
	CBT	OR=0.65 (0.32-1.16)	PBO/Sham	66/9,075	M
	PSOLV	OR=0.77 (0.01-4.40)	WL/NT	66/9,075	M
	CBT	OR=0.77 (0.34-1.48)	WL/NT	66/9,075	M
	FT	OR=0.84 (0.35-1.72)	PBO/Sham	66/9,075	M
	PSD-O	OR=0.96 (0.37-1.93)	PBO/Sham	66/9,075	M
	BT	OR=1.27 (0.19-4.32)	PBO/Sham	66/9,075	M
Suicide attempt/ideation	IPT	OR=0.64 (0.04-2.59)	PBO/Sham	34/NR	M
	CBT	OR=11.31 (0.01-46.11)	PBO/Sham	34/NR	M
	PSD-O	OR=8.64 (0.01-40.05)	PBO/Sham	34/NR	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

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 *(continued)*

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/ patients	Q
Response	Mixed (mood stabilizers and antipsychotics)	**OR=2.24 (z=8.12, p<0.001)**	PBO/Sham	9/1,362	M
	Aripiprazole	**RR=1.86 (1.43-2.43)**	PBO/Sham	2/332	M
	SGAs	**z=10.34, p<0.001**	PBO/Sham	6/1,190	H
	Mood stabilizers	**z=2.06, p=0.04**	PBO/Sham	2/172	M
Acceptability	Aripiprazole	RR=0.80 (0.51-1.27)	PBO/Sham	2/339	M
	Valproate	OR=1.77 (0.83-3.78)	PBO/Sham	2/179	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

RCTs – randomized controlled trials, SMD – standardized mean difference, OR – odds ratio, RR – risk ratio, PBO – placebo, WL – waiting list, NT – no treatment, NR – not reported, NC – not calculable, 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 that 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.

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 disorder 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).

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	**SMD=–0.43 (–0.75 to –0.10)**	PBO/Sham	14/2,502	M
	Fluvoxamine	**SMD=–0.36 (–0.61 to –0.10)**	PBO/Sham	14/2,502	M
	Imipramine	SMD=–0.27 (–0.92 to 0.39)	PBO/Sham	14/2,502	M
	Guanfacine	SMD=–0.13 (–0.39 to 0.12)	PBO/Sham	14/2,502	M
	Fluoxetine	SMD=–0.11 (–0.33 to 0.12)	PBO/Sham	14/2,502	M
	Atomoxetine	SMD=–0.11 (–0.38 to 0.16)	PBO/Sham	14/2,502	M
	Duloxetine	SMD=–0.09 (–0.27 to 0.09)	PBO/Sham	14/2,502	M
	Sertraline	SMD=–0.08 (–0.25 to 0.09)	PBO/Sham	14/2,502	M
	Venlafaxine	SMD=–0.06 (–0.22 to 0.04)	PBO/Sham	14/2,502	M
Efficacy (subject-rated)	Fluoxetine	**SMD=–0.51 (–0.85 to –0.18)**	PBO/Sham	2/154	M
	SNRIs	SMD=–2.14 (–9.75 to 5.48)	PBO/Sham	3/622	M
	Venlafaxine	SMD=–1.71 (–3.93 to 0.51)	PBO/Sham	2/443	M
	SSRIs	SMD=–0.42 (–0.96 to 0.12)	PBO/Sham	4/197	M
	Atomoxetine	SMD=–0.29 (–0.51 to 0.08)	PBO/Sham	2/331	M
	TCAs	SMD= 0.36 (–0.27 to 0.99)	PBO/Sham	2/41	M
Efficacy (parent-rated)	SSRIs	**SMD=–0.82 (–1.38 to –0.27)**	PBO/Sham	2/96	L
Response	Fluvoxamine	**OR=8.17 (1.35-49.40)**	PBO/Sham	19/2,656	M
	Sertraline	**OR=6.05 (2.23-49.40)**	PBO/Sham	19/2,656	M
	Fluoxetine	**OR=4.06 (1.49-18.17)**	PBO/Sham	19/2,656	M
	Guanfacine	OR=5.47 (0.74-49.40)	PBO/Sham	19/2,656	M
	Atomoxetine	OR=4.06 (0.67-24.53)	PBO/Sham	19/2,656	M
	Paroxetine	OR=3.67 (0.67-20.09)	PBO/Sham	19/2,656	M
	Imipramine	OR=3.00 (0.61-14.88)	PBO/Sham	19/2,656	M
	Venlafaxine	OR=2.46 (0.90-6.69)	PBO/Sham	19/2,656	M
	Duloxetine	OR=2.01 (0.37-11.02)	PBO/Sham	19/2,656	M
	Clomipramine	OR=1.22 (0.22-6.69)	PBO/Sham	19/2,656	M
Acceptability	Clomipramine	OR=0.55 (0.02-7.39)	PBO/Sham	20/2,679	M
	Paroxetine	OR=0.61 (0.12-3.32)	PBO/Sham	20/2,679	M
	Fluvoxamine	OR=0.67 (0.11-4.06)	PBO/Sham	20/2,679	M
	Sertraline	OR=0.67 (0.14-2.72)	PBO/Sham	20/2,679	M
	Guanfacine	OR=0.67 (0.10-4.95)	PBO/Sham	20/2,679	M
	Atomoxetine	OR=0.82 (0.15-4.95)	PBO/Sham	20/2,679	M
	Duloxetine	OR=1.00 (0.18-5.47)	PBO/Sham	20/2,679	M
	Venlafaxine	OR=1.11 (0.33-3.67)	PBO/Sham	20/2,679	M
	Fluoxetine	OR=1.65 (0.50-6.69)	PBO/Sham	20/2,679	M
	Imipramine	OR=2.01 (0.37-9.97)	PBO/Sham	20/2,679	M
Remission	Fluoxetine	**RR=2.52 (1.19-5.32)**	PBO/Sham	2/95	L
Suicide attempt/ ideation	Sertraline	**LogOR=–19.8 (–61.7 to 0.7)**	PBO/Sham	9/1,648	M
	Duloxetine	LogOR=0.2 (–2.5 to 2.8)	PBO/Sham	9/1,648	M
	Venlafaxine	LogOR=1.4 (–1.4 to 5.24)	PBO/Sham	9/1,648	M
	Atomoxetine	LogOR=6.6 (–31.6 to 22.7)	PBO/Sham	9/1,648	M
	Guanfacine	LogOR=16.1 (–1.0 to 58.3)	PBO/Sham	9/1,648	M
	Imipramine	LogOR=17.3 (–0.1 to 54.8)	PBO/Sham	9/1,648	M
	Paroxetine	**LogOR=20.0 (1.7 to 60.47)**	PBO/Sham	9/1,648	M

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 *(continued)*

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/patients	Q
Tolerability	Venlafaxine	LogOR=–0.8 (–3.8 to 2.1)	PBO/Sham	15/2,516	M
	Atomoxetine	LogOR=0.0 (–5.3 to 5.3)	PBO/Sham	15/2,516	M
	Duloxetine	LogOR=0.2 (–3.9 to 4.3)	PBO/Sham	15/2,516	M
	Sertraline	LogOR=1.7 (–2.8 to 6.6)	PBO/Sham	15/2,516	M
	Paroxetine	LogOR=1.7 (–2.5 to 6.0)	PBO/Sham	15/2,516	M
	Fluovoxamine	LogOR=2.1 (–2.4 to 7.0)	PBO/Sham	15/2,516	M
	Fluoxetine	LogOR=2.5 (–1.8 to 7.9)	PBO/Sham	15/2,516	M
	Imipramine	LogOR=16.6 (–37.5 to 83.7)	PBO/Sham	15/2,516	M
	Guanfacine	**LogOR=29.2 (2.2-94.3)**	PBO/Sham	15/2,516	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	**SMD=–1.04 (–1.41 to –0.67)**	WL/NT	24/1,239	L
	CBT-Group	**SMD=–0.91 (–1.22 to –0.60)**	WL/NT	27/1,268	L
	CBT	**SMD=–0.67 (–0.88 to –0.47)**	WL/NT	45/2,831	L
	CBT-Child+P	**SMD=–0.45 (–0.67 to –0.23)**	WL/NT	20/1,285	L
	CBT-Individual	**SMD=–0.39 (–0.64 to –0.15)**	WL/NT	21/1,203	L
	CBT	**SMD=–0.31 (–0.51 to –0.11)**	PBO/Sham	15/978	L
	CBT-Parent only	SMD=0.04 (–0.38 to 0.46)	WL/NT	5/307	L
Efficacy (parent-rated)	CBT-Group	**SMD=–0.92 (–1.21 to –0.62)**	WL/NT	21/1,279	L
	CBT-Child only	**SMD=–0.87 (–1.21 to –0.53)**	WL/NT	13/734	L
	CBT	**SMD=–0.70 (–0.90 to –0.51)**	WL/NT	35/2137	L
	CBT-Child+P	**SMD=–0.69 (–0.98 to –0.39)**	WL/NT	17/1,031	L
	CBT-Individual	**SMD=–0.43 (–0.65 to –0.21)**	WL/NT	17/858	L
	CBT-Parent only	SMD=–0.37 (–0.77 to 0.04)	WL/NT	5/372	L
	CBT	SMD=–0.25 (–0.61 to 0.11)	PBO/Sham	8/638	L
Efficacy (mixed-rated)	BT-Group	**SMD=–1.43 (–2.36 to –0.51)**	WL/NT	101/6,625	L
	CBT-Group	**SMD=–1.43 (–1.76 to –1.09)**	WL/NT	101/6,625	L
	BT-Individual+P	**SMD=–1.09 (–1.93 to –0.25)**	WL/NT	101/6,625	L
	CBT-Group+P	**SMD=–0.99 (–1.31 to –0.68)**	WL/NT	101/6,625	L
	CBT-Individual	**SMD=–0.99 (–1.30 to –0.68)**	WL/NT	101/6,625	L
	CBT-Individual+P	**SMD=–0.84 (–1.16 to –0.53)**	WL/NT	101/6,625	L
	CBT-Group	**SMD=–0.76 (–1.16 to –0.36)**	PBO/Sham	101/6,625	L
	CBT-Parent only	**SMD=–0.70 (–1.22 to –0.19)**	WL/NT	101/6,625	L
	CBT-Internet	**SMD=–0.61 (–1.02 to –0.20)**	WL/NT	101/6,625	L
	BT-Individual+Group	SMD=–0.73 (–1.59 to 0.13)	WL/NT	101/6,625	L
	CBT-Individual+Group	SMD=–0.64 (–1.69 to 0.41)	WL/NT	101/6,625	L
	BT-Individual+P	SMD=–0.42 (–1.29 to 0.44)	PBO/Sham	101/6,625	L
	CBT-Group+P	SMD=–0.33 (–0.78 to 0.13)	PBO/Sham	101/6,625	L
	CBT-Individual	SMD=–0.32 (–0.72 to 0.07)	PBO/Sham	101/6,625	L
	CBT-Individual+P	SMD=–0.18 (–0.61 to 0.25)	PBO/Sham	101/6,625	L
	BT-Individual+Group	SMD=–0.06 (–0.94 to 0.82)	PBO/Sham	101/6,625	L
	CBT-Internet	SMD=0.06 (–0.48 to 0.60)	PBO/Sham	101/6,625	L

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 *(continued)*

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/patients	Q
Acceptability	CBT-Individual+Group	OR=0.26 (0.05-5.73)	WL/NT	101/6,625	L
	BT-Individual+P	OR=0.64 (0.22-2.72)	WL/NT	101/6,625	L
	BT-Individual+P	OR=0.81 (0.19-2.27)	PBO/Sham	101/6,625	L
	CBT-Group+P	OR=0.90 (0.46-1.60)	PBO/Sham	101/6,625	L
	CBT-Group	OR=0.85 (0.46-1.44)	PBO/Sham	101/6,625	L
	BT	OR=0.90 (0.32-3.95)	WL/NT	101/6,625	M
	CBT-Individual	OR=0.92 (0.52-1.52)	PBO/Sham	101/6,625	L
	CBT-Group	OR=0.93 (0.57-1.63)	WL/NT	101/6,625	L
	CBT	OR=1.09 (0.85-1.41)	WL/NT	45/3,158	L
	CBT-Group+P	OR=0.99 (0.67-1.55)	WL/NT	101/6,625	M
	CBT	OR=1.00 (0.68-1.49)	PBO/Sham	12/797	L
	CBT-Internet	OR=1.02 (0.42-2.08)	PBO/Sham	101/6,625	L
	CBT-Individual	OR=1.02 (0.67-1.67)	WL/NT	101/6,625	L
	CBT-Internet	OR=1.05 (0.59-2.05)	WL/NT	101/6,625	L
	CBT-Individual+P	OR=1.11 (0.60-1.90)	PBO/Sham	101/6,625	L
	BT-Individual+Group	OR=1.13 (0.28-3.19)	PBO/Sham	101/6,625	L
	BT-Group	OR=1.21 (0.27-22.51)	WL/NT	101/6,625	L
	CBT-Individual+P	OR=1.23 (0.80-2.02)	WL/NT	101/6,625	L
	CBT-Parent only	OR=1.43 (0.75-3.15)	WL/NT	101/6,625	L
Depressive symptoms	CBT	**SMD=–0.34 (–0.51 to –0.17)**	WL/NT	17/1,157	L
	CBT	SMD=–0.18 (–0.45 to 0.09)	PBO/Sham	10/613	L
Functioning	CBT	SMD=–1.03 (–1.38 to –0.68)	WL/NT	11/557	L
Quality of life	CBT-Parent only	**SMD=–1.87 (–3.04 to –0.71)**	WL/NT	101/6,625	L
	CBT-Individual	**SMD=–1.13 (–1.82 to –0.45)**	PBO/Sham	101/6,625	L
	CBT-Individual	**SMD=–1.01 (–1.55 to –0.48)**	WL/NT	101/6,625	L
	CBT-Internet	**SMD=–0.86 (–1.57 to –0.15)**	PBO/Sham	101/6,625	L
	CBT-Group	**SMD=–0.85 (–1.45 to –0.26)**	PBO/Sham	101/6,625	L
	CBT-Individual+P	**SMD=–0.80 (–1.33 to –0.27)**	WL/NT	101/6,625	L
	CBT-Group+P	**SMD=–0.75 (–1.34 to –0.17)**	WL/NT	101/6,625	L
	CBT-Group	**SMD=–0.73 (–1.34 to –0.11)**	WL/NT	101/6,625	L
	CBT-Internet	**SMD=–0.73 (–1.14 to –0.33)**	PBO/Sham	101/6,625	L
	BT-Individual+Group	SMD=–0.79 (–1.68 to 0.09)	WL/NT	101/6,625	L
	BT-Individual+Group	SMD=–0.67 (–1.56 to 0.21)	WL/NT	101/6,625	L
	CBT-Individual+Group	SMD=–0.55 (–1.78 to 0.69)	WL/NT	101/6,625	L
Remission	CBT-Child only	**OR=10.42 (5.84-7.60)**	WL/NT	19/1,184	M
	CBT-Group	**OR=6.25 (4.45-8.78)**	WL/NT	25/1,532	M
	CBT-Remote	**OR=6.14 (2.97-12.71)**	WL/NT	10/591	L
	CBT	**OR=5.45 (3.90-7.60)**	WL/NT	39/2,697	L
	CBT-Individual	**OR=4.53 (2.55-8.03)**	WL/NT	17/1,165	L
	CBT-Individual+P	**OR=4.08 (2.72-6.11)**	WL/NT	19/1,142	M
	CBT-Child only	**OR=3.58 (1.92-6.65)**	PBO/Sham	7/509	L
	CBT-Group	**OR=3.10 (1.14-8.45)**	PBO/Sham	5/353	L
	CBT-Parent only	**OR=2.83 (1.12-7.16)**	WL/NT	4/371	L
	CBT	**OR=2.28 (1.33-3.89)**	PBO/Sham	10/822	L
	CBT-Individual	**OR=2.04 (1.06-3.91)**	PBO/Sham	5/469	L
	CBT-Individual+P	OR=1.12 (0.65-1.92)	PBO/Sham	4/313	L

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 *(continued)*

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/patients	Q
Social anxiety disorder					
Efficacy (subject-rated)	CBT	**SMD=–1.59 (–2.33 to –0.86)**	WL/NT	11/603	L
	BT	**SMD=–1.22 (–2.06 to –0.38)**	WL/NT/PBO/Sham	4/169	L
	CBT	**SMD=–1.19 (–1.72 to –0.67)**	WL/NT/PBO/Sham	14/872	L
	CBT-Group	**SMD=–1.19 (–1.93 to –0.45)**	WL/NT/PBO/Sham	11/670	L
	CBT/BT	**SMD=–1.13 (–1.59 to –0.68)**	WL/NT/PBO/Sham	17/1,016	L
	CBT+P	**SMD=–1.13 (–1.59 to –0.67)**	WL/NT/PBO/Sham	17/983	L
	CBT-Individual	**SMD=–1.10 (–1.91 to –0.29)**	WL/NT/PBO/Sham	3/127	L
	CBT-Individual+Group	**SMD=–0.80 (–1.19 to –0.41)**	WL/NT/PBO/Sham	3/115	L
	CBT-Child only	**SMD=–0.75 (–1.24 to –0.26)**	WL/NT/PBO/Sham	2/70	L
	CBT-Internet	**SMD=–0.52 (–1.01 to –0.03)**	WL/NT/PBO/Sham	2/143	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	**SMD=–0.24 (–0.46 to –0.03)**	PBO/Sham	17/991	L
	Fluoxetine	**SMD=–0.24 (–0.47 to –0.01)**	PBO/Sham	17/991	L
	Clomipramine	SMD=–0.31 (–0.64 to 0.02)	PBO/Sham	17/991	L
	Fluvoxamine	SMD=–0.21 (–0.49 to 0.06)	PBO/Sham	17/991	L
Response	Fluoxetine	**RR=1.49 (1.15-1.96)**	PBO/Sham	2/146	L
	SSRI/TCAs	**RR=1.80 (1.43-2.26)**	PBO/Sham	7/692	L
Acceptability	Fluoxetine	MOR=0.74 (0.25-1.68)	PBO/Sham	18/1,143	L
	Fluvoxamine	MOR=0.79 (0.24-2.07)	PBO/Sham	18/1,143	L
	Sertraline	MOR=0.89 (0.32-2.07)	PBO/Sham	18/1,143	L
	Paroxetine	MOR=1.12 (0.37-3.42)	PBO/Sham	18/1,143	L
	Clomipramine	MOR=3.06 (0.54-21.69)	PBO/Sham	18/1,143	L
Tolerability	SSRIs	**RR=3.59 (1.89-6.84)**	PBO/Sham	7/807	L
Global illness severity	Fluoxetine	**SMD=–0.52 (–0.86 to –0.18)**	PBO/Sham	2/146	L
	SSRIs	**SMD=–0.42 (–0.61 to –0.23)**	PBO/Sham	5/556	M
Remission	SSRIs	**RR=2.06 (1.03-4.13)**	PBO/Sham	3/302	L
Pharmacological augmentation (in SSRI-refractory cases)					
Response	Risperidone	**OR=6.35 (1.48-27.3)**	PBO/Sham	3/72	M
	Quetiapine	OR=2.33 (0.88-6.20)	PBO/Sham	3/102	M
	Olanzapine	OR=2.74 (0.34-21.9)	PBO/Sham	2/70	L
Psychosocial interventions					
Efficacy (clinician-rated)	CBT	**SMD=–0.78 (–1.05 to –0.51)**	WL/NT	17/991	L
	BT	**SMD=–0.72 (–1.20 to –0.24)**	WL/NT	17/991	L
	CBT	SMD=–0.23 (–0.56 to 0.11)	PBO/Sham	17/991	L
Response	CBT/BT-ERP	**RR=3.93 (2.52-6.14)**	WL/NT/PBO/Sham	6/236	L

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 *(continued)*

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/patients	Q
Acceptability	CBT	MOR=0.49 (0.09-2.40)	PBO/Sham	18/1,143	L
	BT-ERP	RR=0.80 (0.35-1.84)	PBO/WL	6/301	L
	CBT	MOR=0.86 (0.23-3.24)	PBO/Sham	18/1,143	L
	CBT	MOR=0.94 (0.21-4.79)	WL/NT	18/1,143	L
	BT	MOR=14.28 (0.87-785.20)	WL/NT	18/1,143	L
Functioning (subject-rated)	CBT	**SMD=–1.15 (–2.11 to –0.19)**	WL/NT	3/194	L
Functioning (parent-rated)	CBT	**SMD=–0.95 (–1.61 to –0.28)**	WL/NT	3/194	L
	CBT	SMD=–0.31 (–0.63 to 0.01)	PBO/Sham	2/183	L
Remission	CBT	**RR=2.33 (1.33-4.00)**	WL/NT	4/271	L
	CBT	**RR=1.59 (1.28-1.96)**	PBO/Sham	3/153	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	**SMD=–1.34 (–1.79 to –0.89)**	WL/NT	3/98	L
	EMDR	SMD=–0.61 (–1.96 to 0.74)	WL/NT	2/65	L
	NET	SMD=–0.57 (–1.23 to 0.09)	WL/NT	2/79	L
Response	CBT	**OR=8.64 (2.01-37.14)**	WL/NT	2/49	L
	NET	OR=3.82 (0.67-21.8)	WL/NT	2/78	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	**RR=1.22 (1.02-1.45)**	PBO/Sham	2/98	L
	Imipramine	**RR=1.35 (1.11-1.64)**	PBO/Sham	12/831	L
Psychosocial interventions					
Efficacy	BT-Alarm	**SMD=–1.30 (–2.16 to –0.44)**	WL/NT	4/127	L
Response	BT-Alarm	**RR=7.23 (1.40-37.77)**	WL/NT	18/827	L
	BT-Alarm	**RR=1.59 (1.16-2.17)**	PBO/Sham	2/181	L
	BT-Reward	**RR=1.22 (1.03-1.45)**	WL/NT	2/325	L

RCTs – randomized controlled trials, 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 that 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

RCTs – randomized controlled trials, 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 that 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.

DISCUSSION

Pooling top-tier evidence from 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 (see supplementary information for further details).

Considered together with a complementary umbrella review published in this journal[14], 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 safety[14]. 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 (parent-child interaction therapy), to

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	**SMD=–0.24 (–0.44 to –0.05)**	Methylphenidate	46/NR	H
	Methylphenidate	**SMD=–0.22 (–0.39 to –0.05)**	Atomoxetine	46/NR	H
Efficacy (parent-rated)	Methylphenidate	**SMD=–1.07 (–1.74 to –0.40)**	Bupropion	23/NR	H
	Methylphenidate	**SMD=–0.23 (–0.37 to –0.10)**	Atomoxetine	23/NR	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	**OR=4.76 (2.50-9.09)**	BT	113/19,398	M
	BT+stimulants	**OR=4.58 (2.49-8.75)**	Stimulants	113/19,398	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	**OR=2.80 (1.50-5.40)**	Desmopressin	15/1,350	M
	Imipramine+oxybutynin	**RR=1.47 (1.09-2.00)**	Imipramine	2/101	L
	Imipramine+oxybutynin	**RR=1.46 (1.06-2.01)**	Oxybutynin	2/100	L
	Desmopressin+BT-Alarm	**RR=1.32 (1.08-1.62)**	Desmopressin	5/359	L
Relapse	Oxybutynin+ imipramine	**RR=0.50 (0.30-0.81)**	Oxybutynin	2/81	L
	Oxybutynin+ imipramine	**RR=0.48 (0.31-0.74)**	Imipramine	2/85	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

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) *(continued)*

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/patients	Q
Tolerability	Paroxetine	**OR=0.22 (0.08-0.87)**	Imipramine	34/5,260	M
	Fluoxetine	**OR=0.31 (0.13-0.95)**	Duloxetine	34/5,260	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	**SMD=–1.35 (–2.16 to –0.55)**	Fluphenazine	28/3,003	L
	Clozapine	**SMD=–0.86 (–1.54 to –0.17)**	Olanzapine	28/3,003	L
	SGAs	**SMD=–0.36 (–0.56 to –0.16)**	FGAs	4/243	L
Response	Risperidone	**OR=5.53 (2.01-15.18)**	Haloperidol	28/3,003	L
Tic disorder					
Response	Topiramate	**RR=1.10 (1.02-1.18)**	Haloperidol/ tiapride	14/1,017	M
	Topiramate	**RR=1.09 (1.01-1.19)**	Haloperidol	10/727	L

RCTs – randomized controlled trials, 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 that 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.

the primary efficacy outcome and functioning (social skills training, and behavioral therapy 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, interpersonal therapy is the only psychosocial intervention outperforming placebo. The combination of CBT with fluoxetine also outperformed placebo on the primary efficacy outcome, and was 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 behavioral therapy, 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 intervention[86].

For obsessive-compulsive disorder, fluoxetine and SSRIs as a class should be considered the first-line pharmacological treatment. Among psychosocial interventions, CBT and behavioral therapy with exposure and response prevention are effective options. If fluoxetine/SSRIs are ineffective, a switch to psychosocial interventions should be performed, and vice versa[71].

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 options[118,119].

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 a more tolerable treatment option[102]. Ideally, starting with safer medications minimizing the risk of adverse events and maximizing adherence is a recommended strategy[14].

For bipolar disorder, little meta-analytic evidence is available overall. For mania, the only positive data are available for aripipra-

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	**SMD=–0.37 (–0.66 to –0.09)**	Mixed	14/727	L
	BT	**SMD=–0.35 (–0.50 to –0.19)**	Mixed	19/1,430	L
Efficacy (teacher-rated)	ST	**SMD=–0.26 (–0.52 to –0.01)**	Mixed	6/615	L
Efficacy (parent-rated)	BT-Parental	**SMD=–0.65 (–1.05 to –0.25)**	TAU/WL/LIP	8/399	L
	ST	**SMD=–0.56 (–0.74 to –0.38)**	Mixed	10/934	L
Aggressive behavior	BI	**SMD=–0.40 (–0.71 to –0.10)**	Mixed	5/350	L
Functioning: academic	ST	**SMD=–0.33 (–0.51 to –0.14)**	Mixed	7/695	L
	BT	**SMD=–0.28 (–0.59 to –0.06)**	Mixed	9/817	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-rated)	PCIT	**SMD=–0.22 (–0.36 to –0.09)**	Mixed	13/846	L
Efficacy: language (mixed-rated)	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	**SMD=–0.55 (–0.99 to –0.11)**	TAU/WL	2/88	L
	PCIT	**SMD=–0.41 (–0.68 to –0.14)**	Mixed	3/215	L
Functioning: social skills	SST-Computer	**SMD=–0.93 (–1.29 to –0.57)**	TAU/WL	5/138	L
	SST	**SMD=–0.83 (–1.07 to –0.60)**	TAU/WL	18/1,266	L
	SST-Face to face	**SMD=–0.81 (–1.08 to –0.53)**	TAU/WL	14/1,128	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- rated)	CBT	**SMD=–0.53 (–0.82 to –0.24)**	Mixed	11/809	M
Oppositional defiant disorder (ODD)					
Efficacy (mixed-rated)	BI	**SMD=–0.79 (–0.93 to –0.64)**	WL/AC	17/NR	L
Tourette's disorder					
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- rated)	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-rated)	BI	**SMD=–0.52 (–0.68 to –0.36)**	WL/AC	10/881	L

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

Outcome	Intervention	Effect size (95% CI)	Control	Number of RCTs/ patients	Q
Efficacy: ODD symptoms (mixed- rated)	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

RCTs – randomized controlled trials, 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 that intervention is more effective than control.

zole, yet lithium is also an evidence-based treatment based on RCT evidence[120]. 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 adults[121], 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 RCTs[122,123], 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.

Among the 104 included meta-analyses, virtually none 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 when they 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 controls, 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) is that such interventions might be preferred to other superior treatments, delaying response and remission[121].

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 youth[125,126], 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 journal[14]. Such detailed data are not generally reported for psychosocial interventions, which is currently a major unmet need[127].

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 adults[128]. 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 concerning 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.

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