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## The future of child and adolescent clinical psychopharmacology: A systematic review of phase 2, 3, or 4 randomized controlled trials of pharmacologic agents without regulatory approval or for unapproved indications

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## ABSTRACT

We aimed to identify promising novel medications for child and adolescent mental health problems. We systematically searched <https://clinicaltrials.gov/> and <https://www.clinicaltrialsregister.eu/> (from 01/01/2010–08/23/2022) for phase 2 or 3 randomized controlled trials (RCTs) of medications without regulatory approval in the US, Europe or Asia, including also RCTs of dietary interventions/probiotics. Additionally, we searched phase 4 RCTs of agents targeting unlicensed indications for children/adolescents with mental health disorders. We retrieved 234 ongoing or completed RCTs, including 26 (11%) with positive findings on  $\geq 1$  primary outcome, 43 (18%) with negative/unavailable results on every primary outcome, and 165 (70%) without publicly available statistical results. The only two compounds with evidence of significant effects that were replicated in  $\geq 1$  additional RCT without any negative RCTs were dasotraline for attention-deficit/hyperactivity disorder, and carbetocin for hyperphagia in Prader-Willi syndrome. Among other strategies, targeting specific symptom dimensions in samples stratified based on clinical characteristics or established biomarkers may increase chances of success in future development programmes.

## 1. Introduction

The treatment of child and adolescent mental health conditions includes pharmacological and non-pharmacological options, such as psychological therapies (Correll et al., 2021). Although not every mental health condition may be amenable to pharmacological treatment, we lack evidence-based effective pharmacological options for the core symptoms of several prominent conditions frequently managed by child and adolescent mental health services, such as autism spectrum disorder

(ASD), posttraumatic stress disorder (PTSD) and anorexia nervosa. The most comprehensive umbrella review (Correll et al., 2021) on efficacy and acceptability of medications in child and adolescent mental health found the strongest support [in terms of highest effect sizes (ESs)] for the following compounds: amphetamine and methylphenidate for core symptoms of attention-deficit/hyperactivity disorder (ADHD); aripiprazole and risperidone for irritability in ASD; risperidone for aggression in disruptive behavior disorders; risperidone, olanzapine, paliperidone, and ziprasidone for symptoms of schizophrenia; fluoxetine for depression; aripiprazole for manic symptoms in bipolar disorder; fluoxetine for anxiety; and fluoxetine/other selective serotonin reuptake inhibitors (SSRIs) for obsessive-compulsive disorder (OCD). A related umbrella review (Solmi et al., 2020) focusing on safety found that the best tolerability/safety profile emerged for escitalopram and fluoxetine (for

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depression), lurasidone (for schizophrenia), methylphenidate (for ADHD), and lithium (for bipolar disorder, manic episode). Concerns were identified in relation to the safety profile of venlafaxine, olanzapine, atomoxetine, guanfacine, and valproate.

Even for disorders for which effective medications are available for their core symptoms, pharmacological options for associated problems are suboptimal. For instance, psychostimulants for core symptoms of ADHD (Cortese, 2020) are the most efficacious medications, at least in the short-term, in psychiatry and among the most efficacious medications across all the medical disciplines (Leucht et al., 2012). However, the impact of psychostimulants on other aspects related to ADHD is less striking. For instance, their effects on executive dysfunctions (McKenzie et al., 2022) vary according to the type of executive dysfunction and their benefits on emotional dysregulation (Lenzi et al., 2018) are characterized by lower ESs.

There have been concerns that the pace of development of clinical trials and regulatory approval of novel medications in child and adolescent psychiatry is slow, and drug companies are pulling away from the field given the substantial failures in their programmes (Persico et al., 2015). Quantitative evidence is needed to exactly inform how many medications have been successful in phase 2, 3 or 4 RCTs of agents for child and adolescent mental health disorders. Previous reviews have presented medications in the pipeline or not licensed for specific disorders, e.g., ASD (Baribeau et al., 2022) or ADHD (Nageye and Cortese, 2019). However, to our knowledge, no review has systematically assessed novel unlicensed or off-labelled medications across the main mental health disorders in children/adolescents. Here, we aimed to fill this gap by systematically reviewing recent progress and current clinical trial activity, evaluating promising compounds for child and adolescent mental health problems. As dietary or probiotic interventions are chemical substances that may be recommended by some practitioners and are of interest for patients and their families, we also included RCTs focusing on these compounds.

## 2. Methods

The study protocol is available in Open Science Framework, OSF (<https://bit.ly/3EiEi5h>).

### 2.1. Search strategy

We searched <https://clinicaltrials.gov/and> and <https://www.clinicaltrialsregister.eu/> from 01/01/2010–08/23/2022 using search terms related to the mental health conditions of interest for this review (see below). The search was conducted independently by two investigators (KMG and SC). The time frame is similar to the one considered in a recent similar review on phase 2/3 RCTs of psychopharmacological agents in adults (Correll, 2023). We also conducted an additional systematic targeted search in PubMed to check if identified RCTs for which results were not available in the clinical trials platforms had been published. The following filters were used for the search in clinicaltrials.gov: 1) study type: interventional studies (Clinical Trials); 2) recruitment: not yet recruiting/recruiting/enrolling by invitation/active, not recruiting/terminated/completed/unknown status; 3) age group: “Child” (birth-17); 4) phase: phase 2/phase 3 or 4; 5) study start: from 01/01/2010, which, as in the systematic review by Correll et al. (2023) in adults, was deemed adequate to reflect recent developments in the field. We assumed that, if a trial initiated  $\geq 12$  years ago and its results had not been published or no additional studies were ongoing, this trial program had been discontinued.

The following filters were used for the search in <https://www.clinicaltrialsregister.eu/>: 1) select trial status: completed/ongoing/restarted; 2) age range: children and adolescents; 3) select trial phase: phase two/phase three/phase four; and 4) select date range: 2010–01–01 (with the same reasoning for the cut-off date as mentioned for clinicaltrials.gov).

### 2.2. Inclusion and exclusion criteria

We included ongoing or completed phase 2 or 3 RCTs, regardless of their level of blinding, assessing pharmacologic agents, dietary supplements or probiotics that had to the best of our knowledge no regulatory approval in the US, Europe (through EMA licensing procedures, not those approved by individual countries through national licensing procedures) or Asia as of 08/23/2022, for mental health conditions in children or adolescents (all participants aged 18 years or less). We also included phase 4 RCTs of agents approved in psychiatry or other areas of medicine but targeting a currently unapproved mental health indication or an age range different from the one in the approval label in children/adolescents.

We focused on RCTs targeting the following mental health conditions (in alphabetical order): ADHD, Anxiety Disorders, ASD, Bipolar Disorder, Conduct Disorder/Oppositional Defiant Disorder/Disruptive Mood Dysregulation Disorder/Intermittent Explosive Disorder, Depressive Disorder (including Major Depressive Disorder), Eating Disorders, Intellectual Developmental Disorder (Intellectual and Developmental Disability, IDD), OCD, PTSD (the inclusion of this disorder was post hoc in relation to the protocol), Schizophrenia, and Tourette’s Syndrome, accepting any diagnostic definition reported by the study investigators.

We excluded the following interventions: brain stimulation, digital app-based, and psychosocial interventions, except when they were combined with novel pharmacological /dietary treatments. We also excluded any trial program that was listed in the clinical trials registries as having been discontinued or stopped, and RCTs of agents that were abandoned and are not being pursued further based on information in the public domain.

### 2.3. Classification of the mechanisms of action of the tested agents

To classify the possible mechanisms of action of the tested agents, we referred whenever possible to the Neuroscience based Nomenclature (NbN) website (<https://nbn2r.com/>). A version of the NbN is available for medications used in child and adolescent psychiatry, NbN C&A (<https://nbnca.com/>) (Cortese et al., 2022).

### 2.4. Assessment of study characteristics

We aimed to present the academic-sponsored versus the industry-funded RCTs, and, with reference to the results of the systematic review of recent/ongoing RCTs of psychotropics in adults by Correll et al. (2023), a comparison between findings in child/adolescent and adults mental disorders, respectively.

### 2.5. Evaluation of promising compounds

After summarizing the search results, we highlighted those agents and mechanisms of action in each disease category that were considered to be most promising based on the current level of evidence with regard to i) positive phase 2 and/or phase 3 or 4 clinical trials indicating superiority vs. placebo/other control; ii) magnitude of the observed effect, with reference to the benchmarks suggested by Cohen (Cohen, 1988): 0.2: small; 0.5: medium; 0.8: large ESs; iii) demonstration of minimum requirements for safety/tolerability, in terms of lack of severe adverse events as defined by the Food and Drug Administration (FDA), i.e., those: resulting in death, or life threatening, or requiring inpatient hospitalisation or causing prolongation of existing hospitalisation, or resulting in persistent or significant disability/incapacity, or contributing to a congenital anomaly/birth defect, or requiring intervention to prevent permanent impairment or damage; and iv) consistency of findings within a clinical trials program, i.e., positive results across all the RCTs testing the medication.

### 3. Results

We identified 234 RCTs (Supplemental Table 1). For around 29% of these RCTs (n = 69) results for primary efficacy endpoints with statistical analyses were reported; in the rest (71%, n = 165), results with powered statistical analysis of significance were not available (of these: ongoing trials: 46%, completed trials: 40%, unknown status: 7%, terminated: 4%, not yet recruiting: 3%).

RCTs with positive results on at least one primary outcome (n = 26), and those with negative results on every primary outcome (n = 43) are reported in Tables 1–4, grouped by disorder (in alphabetical order). When available, Tables 1–4 report also data on tolerability, in terms of percentage of participants who dropped out due to adverse events or those who experienced adverse events defined as serious by the study authors, in line with the above-mentioned FDA classification.

Fig. 1 shows the number of positive and negative RCTs for each disorder. Fig. 2 reports a bar graph depicting the number of trials for each condition, indicating the portion of academic sponsored versus industry-funded trials. Mechanisms of action of the compounds assessed in at least five RCTs, by conditions and overall, are reported in Fig. 3. A comparison of the number of adult versus child trials by condition is reported in Fig. 4.

The following sections provide a summary of the efficacy and, when available, tolerability results, from the retrieved RCTs, grouped by disorder, in alphabetical order. Availability of trial results refer to the last full check of the databases (08/23/2022).

#### 3.1. Attention-deficit/hyperactivity disorder (ADHD)

Thirty-nine RCTs were included. Overall, 50% of these RCTs were funded by drug companies, and 50% were sponsored by universities/hospitals. When limiting to RCTs of pharmacological agents, 71% and 29% were funded by drug companies and sponsored universities/hospitals, respectively. Fourteen mechanisms of action were assessed, including 25 compounds. Mechanisms of action of the pharmacological agents assessed in RCTs in ADHD included the following:

1. Inhibition of dopamine and noradrenergic transport and increase in vesicular dopamine release (lisdexamfetamine dimesylate, n = 1; which is approved by the FDA and other regulatory bodies for ≥6-year-olds but the retained RCT tested it in 4–5-year-olds)
2. Inhibition of dopamine and noradrenergic transport (methylphenidate immediate release, n = 2; FDA-approved for children aged ≥6 years old, but tested in one RCT in children aged 3–5 years old and in another RCT to augment Brief Early Intervention + Parent Training + Adolescent CBT; Aptensio extended release (XR) methylphenidate, n = 1; similarly, tested in one RCT in children aged 4–6 years old)
3. Alpha2-noradrenergic receptor agonism (AR08, n = 1)
4. Serotonin, norepinephrine, and dopamine reuptake inhibition (dasotraline, n = 3; centanafadine, n = 2)
5. NMDA-type glutamate receptor antagonism (amantadine, n = 1)
6. Glutamate receptor agonism (fasoracetam monohydrate, n = 3; note: tested in children/adolescents with ADHD with and without genetic mutation of the metabotropic glutamate receptor)
7. Histaminergic, muscarinic, and serotonergic receptor antagonism (cyproheptadine, n = 1)
8. Glycine transporter I inhibition (GlyTI-M, n = 1)
9. Melatonin receptor agonism (melatonin, n = 2; note: for ADHD-related sleep problems and ADHD core symptoms)
10. Acceleration of the metabolic degradation of ethanol and prevents adenosine triphosphate (ATP) inactivation (metadoxine extended-release ER, n = 1)
11. Inhibition of G protein-coupled inwardly-rectifying potassium channels: tipepidine hibenzate (n = 1)

12. Dopaminergic (1/2) receptor antagonism (molindone, n = 3; note: tested for comorbid aggression)
13. We also found a RCT (n = 1) of an agent [Prospecta (MMH-MAP)] tested in Russia for which we could not find any specific information on the mechanism of action.

Other RCTs tested the following: probiotics (n = 3), carnitine (n = 1), coenzyme Q, as an antioxidant, added to atomoxetine (n = 1), omega-3 fatty acids (n = 3), pycnogenol (n = 1), superba krill oil (n = 1), tocotrienols (n = 1), vitamin A (n = 1), ginkgo extract (n = 2), and various micronutrients (n = 2).

Available results show the following pharmacological agents were significantly better than placebo/control in terms of improvement of ADHD core symptom severity: dasotraline 4 mg [in one RCT - NCT02428088 (n = 112 on dasotraline 2 mg/day, n = 115 on dasotraline 4 mg/day, n = 116 on placebo) with a mean ES of 0.48 (95% CI not reported) whereas for another RCT - NCT02734693 (n = 20 on dasotraline 6 mg/d; n = 56 on dasotraline 4 mg/d; n = 56 on placebo) results only indicated superiority but ES was not reported] and 2 mg in one RCT (NCT03231800, n = 47 on dasotraline 2 mg/day; n = 47 on placebo) but not in another one (NCT02428088) – of note, the development program of dasotraline for ADHD was halted by the manufacturer in 2020; lisdexamfetamine dimesylate for 4–5-year-olds (5, 10, 20, 30 mg: n = 40, 37, 37 and 39, respectively; placebo: n = 4; ES: 0.43 (95% CI not reported).

As for tolerability, in one study of dasotraline (NCT02428088) discontinuation rates due to adverse events were higher in the dasotraline 4 mg/day arm (12.2%) compared with the 2 mg/day arm (6.3%) and placebo (1.7%). There were no serious adverse events or clinically meaningful changes in blood pressure or heart rate with dasotraline and lisdexamfetamine was generally well tolerated.

Furthermore, one study showed that coenzyme Q was effective when added to atomoxetine (decreasing total ADHD symptom severity on the Conners parent-rating scale by about 34%, vs. 18% in the atomoxetine only group, ES not reported). Finally, in another RCT, treatment with micronutrients improved one of the primary outcomes (the clinical Global Impression Scale-CGI, ES not reported) but not the other primary outcome as labelled by the authors (parents' rating of ADHD symptoms).

Two (out of three) RCTs of fasoracetam showed no significant effects on the primary outcome (results were not available, yet in the third RCT). Likewise, omega-3 fatty acids were not superior to placebo in the only RCT that reported results.

Results with statistical analyses from the RCTs of the other agents were not available.

#### 3.2. Anxiety disorders

Seven RCTs were retained. Altogether, 29% were funded by drug companies and 71% were sponsored by universities/hospitals. One RCT focused on generalized anxiety disorder exclusively, the others recruited participants with a variety of anxiety disorders (mainly generalized, social and/or separation anxiety disorder). Two mechanisms of action were assessed, including 4 compounds. Mechanisms of action of the compounds assessed in RCTs in anxiety disorders include:

1. Selective serotonin reuptake inhibition (escitalopram, n = 3; sertraline, n = 1; fluoxetine, n = 1; and another RCT comparing fluoxetine, sertraline, or escitalopram to Cognitive Behavioral Therapy [CBT])
2. Noradrenergic (alpha-2) receptor agonism (guanfacine extended release [XR], n = 1)

The RCT of guanfacine XR showed no significant differences in the scores of the exploratory efficacy measures (Pediatric Anxiety Rating Scale [PARS] and Screen for Child Anxiety Related Emotional Disorders [SCARED]) although at endpoint, more participants assigned to

**Table 1**  
Retrieved RCTs with positive or negative findings for attention-deficit/hyperactivity disorder and anxiety disorders.

| Compound/Dose  | Mechanism of Action   | Total n of active arms | Control              | Total n subjects | Age range | Trial Duration | Funding/Manufacturer                                       | Phase  | NCT/EUDRACT number | Country            | Start date     | Descriptive Results (primary outcome)       | Comments   |
|--|---|------------------------|----------------------|------------------|-----------|----------------|--|--|--------------------|--------------------|----------------|---|--|
| <b>ADHD</b>  |   |                        |                      |                  |           |                |  |  |                    |                    |                |   |  |
| Coenzyme Q + Atomoxetine, doses not specified          | Coenzyme antioxidant + norepinephrine reuptake inhibitor                    | 2                      | Placebo + Coenzyme Q | 40               | 2–18      | 6 months       | Sherief Abd-Elsalam, Tanta University                      | 3  | NCT04216186        | Egypt              | November 2018  | Superior                                    | Efficacy: CPRS-48 total score improvement in 34% with atomoxetine + CoQ vs. in 18% with atomoxetine + placebo<br>Results in: doi: 10.2174/1871527320666211124093345  |
| Dasotraline (SEP-225289) 2 mg/day; 4 mg/day            | Serotonin-norepinephrine-dopamine reuptake inhibitor (SNDR)                 | 2                      | Placebo              | 330              | 6–12      | 42             | Sunovion   | 2–3  | NCT02428088        | USA                | April 2015     | Superior (4 mg)                             | Efficacy: Change from baseline in ADHD-RS-IV at week 6:<br>ES (4 mg/d vs. placebo): 0.84<br>ES (2 mg/d vs. placebo): 0.03<br>Tolerability: 6.3%, 12.2% and 1.7% participants discontinued due to treatment-emergent AE in the dasotraline 2 mg/day, dasotraline 4 mg/day and placebo arm, respectively<br>Results reported in doi: 10.1089/cap.2018.0083 |
| Dasotraline 2 mg/day                                   |   | 2                      | Placebo              | 95               | 6–12      | 15             | Sunovion   | 3  | NCT03231800        | USA                | July 2017      | Superior                                    | Efficacy: SKAMP-score at day 15<br>ES: 1.04<br>Tolerability: 0 serious AE in both arms   |
| Dasotraline 4 and 6 mg/day                             |   | 1                      | Placebo              | 132              | 6–12      | 15             | Sunovion   | 3  | NCT02734693        | USA                | April 2016     | Superior (4 mg/day)                         | Efficacy: SKAMP-score at day 15: 4 mg/d vs. Placebo p < 0.001 - ES not reported. 6 mg/d-arm discontinued.<br>Tolerability: 0 serious AE in both dasotraline arms; 1 serious AE (1.795) in placebo arm  |
| Fasoracetam (AEVI-001)                                 | Glutamate receptor agonist  | 1                      | Placebo              | 69               | 6–17      | 42             | Aevi Genomic Medicine, LLC, a Cerecor company  Cerecor Inc | 2  | NCT03265119 Part A | USA                | August 2017    | No effect                                   | In children and adolescents with ADHD and without mGluR mutations<br>Tolerability: 1 (2.94%) and 0 serious AE in fasoracetam and placebo arm, respectively   |
|  |   | 1                      | Placebo              | 109              | 6–17      | 42             |  | Aevi Genomic Medicine, LLC, a Cerecor company  Cerecor Inc | 2                  | NCT03609619 Part B | USA            | August 2018                                 | No effect  |
| Lisdexamfetamine dimesylate (SPD489) 5,10,20,30 mg/day | Inhibits dopamine and NE transporters; increases vesicular dopamine release | 1                      | Placebo              | 199              | 4–5       | 42             | Shire Takeda   | 3  | NCT03260205        | USA                | September 2017 | Superior                                    | FDA approved in ≥ 6 year-old. This RCT recruited in 4–5 year-old<br>Efficacy: Improvement in ADHD-RS-IV at week 6: ES: 0.43<br>Tolerability: 0 serious AE in either arm  |
| Micronutrient capsules, dose not specified             | Unknown   | 1                      | Placebo              | 135              | 6–12      | 112            | Oregon Health and Science University                       | 31–1   | NCT03252522        | USA-Canada         | April 2018     | Superior on one of the two primary outcomes | Investigational product is Broad Spectrum Micronutrients; a 36-ingredient blend of vitamins, minerals, amino acids, and antioxidants.<br>Efficacy: CGI-I response in 54% of the  |

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Table 1 (continued)

| Compound/Dose   | Mechanism of Action  | Total n of active arms | Control | Total n subjects | Age range | Trial Duration | Funding/Manufacturer                                  | Phase | NCT/EUDRACT number | Country | Start date   | Descriptive Results (primary outcome) | Comments   |
|---|--|------------------------|---------|------------------|-----------|----------------|---|-------|--------------------|---------|--------------|---------------------------------------|--|
| Omega-3 Fatty Acids; DHA Richoil 250 mg pearl (DMF srl) twice daily | Alters arachidonic acid metabolism and oxidative reactions | 1                      | Placebo | 50               | 6–14      | 6 months       | IRCCS Eugenio Medea/DMF srl (Dietetic Metabolic Food) | 3     | NCT01796262        | Italy   | June 2012    | Not superior                          | micronutrient group and in 18% of the placebo group ( $p < 0.001$ ).<br>Tolerability: No serious AEs in either arms<br>Results in 10.1016/j.jaac.2021.07.005<br>Efficacy: Change in ADHD-RS-IV after 6 months: ES = 0.09<br>Tolerability: No serious AEs in either arms<br>Results available at: doi: 10.1007/s00787-018-1223-z                              |
| <b>ANXIETY DISORDERS</b>  |  |                        |         |                  |           |                |   |       |                    |         |              |                                       |  |
| Guanfacine, 1–6 mg/d  | Second generation alpha-2 agonist                          | 1                      | Placebo | 83               | 6–17      | 84             | Shire   | 2     | NCT01470469        | USA     | January 2012 | Not superior                          | For generalized, social and/or separation anxiety disorder<br>Efficacy: No difference in PARS, SCARED, or CGI-I-scores at week 12. ES not reported.<br>Tolerability: In the guanfacine arm, 8 (12.9%) individuals discontinued due to AE (not specified how many in the placebo arm). No serious AEs in either arms<br>Results in doi: 10.1089/cap.2016.0132 |

Legend: ADHD-RS-IV=ADHD Rating Scale-IV; AE=Adverse event; CGI-I=Clinical Global Impression-Improvement; ES=Effect size; FDA=US Food and Drug Administration; mGluR=Metabotropic glutamate receptor; PARS=Pediatric Anxiety Rating Scale; RCT=Randomized Controlled Trial; SCARED=Screen for Child Anxiety Related Emotional Disorders; SKAMP=Swanson, Kotkin, Agler, M-Flynn, Pelham Rating Scale.

**Table 2**  
Retrieved RCTs with positive or negative findings for autism spectrum disorder.

| Compound/Dose   | Mechanism of Action                                 | Total n of active arms | Control | Total n subjects | Age range | Trial Duration | Funding/Manufacturer  | Phase | NCT/EUDRACT number          | Country     | Start date   | Descriptive Results (primary outcome) | Comments   |
|---|---|------------------------|---------|------------------|-----------|----------------|---|-------|-----------------------------|-------------|--------------|---------------------------------------|--|
| Bumetanide (S95008), 0.5 mg BID   | Decreases the reabsorption of sodium by the kidneys | 1                      | Placebo | 211              | 2–6       | 6 months       | Institut de Recherches Internationales Servier                | 3     | NCT03715153; 2017–004420–30 | Multiple    | October 2018 | Not superior                          | Efficacy: Childhood Autism Rating Scale, Second Edition (CARS2) total raw score from baseline to 6 months. P-value for group difference $p = 0.62$ . Tolerability: serious AE in 6.54% and 2.88% of participants in bumetanide and placebo arms, respectively  |
| Bumetanide 0.5 mg/ml, dose not specified  |   | 2                      | Placebo | 92               | 7–15      | 91             | Brain Center Rudolf Magnus, University Medical Center Utrecht | 2     | 2014–001560–35              | Netherlands |              | Not superior                          | Efficacy: Bumetanide not superior to placebo on the Social Responsiveness Scale (SRS) at 91 days (mean difference $-3.16$ , 95% CI = $-9.68$ to $3.37$ , $p = 0.338$ ). Tolerability: 2 (4.2%) and 1 (2.2%) patients in the bumetanide and placebo arm, respectively, had serious AE. Reported in in DOI: 10.1016/j.jaac.2020.07.888 |
| Bumetanide 0.5, 1.0 or 2.0 mg BID, or 0.02, 0.04 or 0.08 mg/kg BID if bodyweight < 25 kg. |   | 3                      | Placebo | 91               | 2–18      | 6 months       | Neurochlore   | 2     | 2013–003259–39              | France      | January 2014 | Not superior                          | Efficacy: Bumetanide not superior to placebo on change in CARS from baseline to Day 90 (ES not reported, group difference $p = 0.69$ ). Tolerability: 1 (5%), 1 (4.35%), 2 (9.09%), and 0 serious AE in the bumetanide low, medium, high dose and placebo arms, respectively   |
| Bumetanide 1 mg/day   |   | 1                      | Placebo | 60               | 3–10      | 90             | University Hospital, Brest                                    | 3     | NCT01078714                 | France      | March 2010   | Superior                              | Efficacy: Bumetanide superior, compared to placebo, on change in Child Autism Rating Scale score from day 0 to day 90 (No ES reported, group difference $p0.0044$ ). Tolerability: 2 (6.6%) patients on bumetanide and 2 (6.6%) on placebo had serious AE. Reported in: doi: 10.1038/tp.2012.124                                     |
| D-cycloserine, 50 mg/day  | GABA transaminase                                   | 1                      | Placebo | 68               | 5–11      | 154            | Indiana University United States                              | 3     | NCT01086475                 | USA         | March 2010   | Not superior at wk 11, but            | Efficacy: No change from baseline to week 11 in Social Responsiveness Scale (SRS)  |

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Table 2 (continued)

| Compound/Dose                           | Mechanism of Action  | Total n of active arms | Control | Total n subjects | Age range | Trial Duration | Funding/Manufacturer                      | Phase | NCT/EUDRACT number | Country | Start date    | Descriptive Results (primary outcome) | Comments   |
|---|--|------------------------|---------|------------------|-----------|----------------|---|-------|--------------------|---------|---------------|---------------------------------------|--|
|   | inhibitor and antibiotic   |                        |         |                  |           |                | Department of Defense                     |       |                    |         |               | superior at wk 22                     | compared to placebo (No ES reported, $p = 0.45$ ). At wk22, the difference between groups was significant on the SRS ( $p = 0.042$ ).<br>Tolerability: 0 and 1 (3%) serious AE in the D-cycloserine and placebo group, respectively<br>Data reported in DOI: 10.1186/s13229-015-0062-8 and DOI: 10.1186/s13229-017-0116-1  |
| Everolimus, 5–10 ng/ml                  | Kinase inhibitor   | 1                      |         | 60               | 4–15      | 12 months      | Erasmus Medical Center Utrecht University | 2/3   | NCT01730209        | NL      | November 2012 | Not superior                          | Patients with autism, tuberous sclerosis complex and $IQ < 80$ .<br>Efficacy: No benefit on cognitive ability measured by IQ at 12 months (treatment effect $-5.6$ IQ points, 95%CI: $-12.3$ to $1.0$ ).<br>Tolerability: 2 (13.3%) patients on everolimus and 2 (11.7%) on placebo discontinued due to AEs<br>Results reported in doi: 10.1212/WNL.0000000000007749 |
| Folinic acid (Folinoral), 10 mg/day     | Counteracts the effects of folic acid antagonists and enhance the effects of fluoropyrimidines | 1                      | Placebo | 40               | 3–10      | 84             | Central Hospital, Nancy, France           | 2     | NCT02551380        | France  | October 2015  | Superior                              | Efficacy: Greater change in ADOS global score at 12 weeks with folinic acid, than with placebo ( $-2.78$ vs. $-0.4$ points, $P = 0.020$ ).<br>Tolerability: no serious AE reported<br>Results in: doi: 10.1016/j.biochi.2020.04.019.   |
| Guanfacine XR (Intuniv), up to 4 mg/day | Second-generation alpha-2 agonist  | 1                      | Placebo | 62               | 5–14      | 56             | Yale University                           | 4     | NCT01238575        | USA     | Dec 2011      | Superior to placebo                   | Pervasive development disorder<br>Efficacy: Superior on the parent-rated Hyperactivity subscale of the Aberrant Behavior Checklist (ABC) at week 8 ( $ES = 1.4$ ; $p < 0.001$ ).<br>Tolerability: 1 (3.3%) and 0 serious AE in the guanfacine and placebo arm, respectively<br>Results in doi: 10.1089/cap.2006.16.589   |

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Table 2 (continued)

| Compound/Dose  | Mechanism of Action  | Total n of active arms | Control | Total n subjects | Age range | Trial Duration | Funding/Manufacturer   | Phase | NCT/EUDRACT number          | Country | Start date     | Descriptive Results (primary outcome)                        | Comments  |
|--|--|------------------------|---------|------------------|-----------|----------------|--|-------|-----------------------------|---------|----------------|--|---|
| Lurasidone 20 and 60 mg/day daily  | Dopamine D2, 5-HT2A, 5-HT7, alpha2A- and alpha2C-adrenoceptor antagonist | 2                      | Placebo | 150              | 6–17      | 42             | Sunovion   | 3     | NCT01911442                 | USA     | August 2013    | Not superior   | Efficacy: Not significant change in Aberrant Behavior Checklist (ABC) Irritability Subscale Score at Week 6 with 60 mg/d ( $p = 0.36$ ) or 20 mg/d ( $p = 0.55$ ), compared to placebo. Tolerability: 3 (6.1%), 2 (3.9%) and 0 serious AE in the low dose lurasidone, high dose lurasidone, and placebo arms, respectively<br>Results in doi: 10.1007/s10803-015-2628-x   |
| Melatonin (NPC-15), 1 mg or 4 mg at bedtime  | MT1 and MT2 receptor agonist, 5-HT2C receptor antagonist                 | 2                      | Placebo | 196              | 6–15      | 70             | Nobelpharma  | 1–3   | NCT02757066                 | Japan   | June 2016      | Superior at dose of 4 mg. No results available for 1 mg arm. | Efficacy: Significant shortening of sleep onset latency by electronic sleep diary at week 2 with 4 mg/d, compared to placebo (No ES reported, $p < 0.0001$ ). Tolerability: all treatment-emergent AE were mild<br>Results in doi: 10.1186/s12888-020-02847-y   |
| Memantine, full dose vs reduced dose. Full dose: 3–15 mg/day dependent on bodyweight. Reduced dose: 3–6 mg/day | Glutamate receptor antagonist  | 2                      | Placebo | 479              | 6–12      | 84             | Forest Laboratories  | 2     | NCT01592747; 2012-001568-31 | USA     | September 2012 | Not superior   | Efficacy: No difference in proportion of Patients Meeting the Criterion for Loss of Therapeutic Response (LTR) by week 12 ( $p = .66-0.78$ ). LTR is defined by worsening (increase) of at least 10 points in Social Responsiveness Scale (SRS) total raw score relative to the Visit 1 (randomization) score. Tolerability: 1 (0.06%), 0, and 0 serious AE in the memantine reduced dose, full dose and placebo arms, respectively |
| Memantine from 3 mg to 12 mg/day   |  | 1                      | Placebo | 23               | 6–12      | 168            | Icahn School of Medicine at Mount Sinai Rush University Medical Center  Nationwide Children's Hospital | 2     | NCT01372449                 | USA     | December 2011  | Not superior   | Efficacy: No significant difference in (A) Change in Developmental Neuropsychological Assessment (NEPSY) Apraxia and Repetition of Nonsense Words Subtests from baseline to weeks 12 and 24, and (B) change in Expressive Vocabulary Test (EVT) from baseline to weeks 12 and 24  |

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Table 2 (continued)

| Compound/Dose   | Mechanism of Action   | Total n of active arms | Control | Total n subjects | Age range | Trial Duration | Funding/ Manufacturer   | Phase | NCT/ EUDRACT number | Country     | Start date    | Descriptive Results (primary outcome) | Comments   |
|---|---|------------------------|---------|------------------|-----------|----------------|---|-------|---------------------|-------------|---------------|---------------------------------------|--|
| Metformin, 250 mg once daily- 850 mg twice daily                                | Inhibits mitochondrial respiratory chain; activates AMP-activated protein kinase  | 1                      | Placebo | 60               | 6–17      | 112            | Massachusetts General Hospital  Vanderbilt University  University of Pittsburgh  Nationwide Children's Hospital Ohio State University | 3     | NCT01825798         | USA- Canada | April 2013    | Superior to placebo                   | (No ES reported, p-values from 0.32 to 0.96).<br>Tolerability: no serious AE in either arms<br>Results in doi: 10.1089/cap.2021.0010<br>For the treatment of overweight Induced by Antipsychotic Medication in Young People With ASD. Efficacy: Significant increase in change in Body Mass Index Z-score from baseline to week 16 (ES=0.82, p = 0.003).<br>Tolerability: 1 (3.1%) serious AE with placebo<br>Results in doi: 10.1001/jamapsychiatry.2016.1232 |
| Methylcobalamin (Methyl B12) 75 µg/Kg subcutaneously injected once every 3 days | Enhances myelin production  | 1                      | Placebo | 57               | 3–7       | 56             | University of California, San Francisco   | 1–3   | NCT01039792         | USA         | January 2010  | Superior to placebo                   | Efficacy: Significant change in Clinical Global Impression-Improvement (CGI-I) from baseline to week 8 (ES=0.84, p = 0.005).<br>Tolerability: no serious AE in either arms.<br>Results in doi: 10.1089/cap.2015.0159   |
| Mirtazapine, up to 15 mg/week   | Antagonist of alpha 2 A, alpha 2B, and alpha 2 C adrenergic receptors, serotonergic 5-HT 2a and 2 C receptors, and histamine H1 receptors | 1                      | Placebo | 30               | 5–17      | 70             | Massachusetts General Hospital  Autism Speaks   | 3     | NCT01302964         | USA         | August 2010   | Not superior                          | Efficacy: Non-significant decreases in (A) Mean 10-Week Change in Pediatric Anxiety Rating Scale 5-Item Total Score (ES=0.64, p = 0.63), and (B) Proportion of Participants who Responded to Treatment at 10 Weeks According to the Improvement Item of the Clinical Global Impression-Scale (Response Defined as CGI-I=1 or CGI-I=2 (47% vs. 20%).<br>Tolerability: no serious AE in either arms.<br>Results in doi: 10.1038/s41386-022-01295-4               |
| Omega-3 fatty acids (Nutra Sea HP), 1.5 g of EPA + DHA daily                    | Alters arachidonic acid metabolism and oxidative reactions  | 1                      | Placebo | 38               | 2–5       | 168            | Holland Bloorview Kids Rehabilitation Hospital, The Hospital for Sick Children  | 2     | NCT01248728         | Canada      | November 2010 | No effect                             | Efficacy: There was no significant difference between groups on the 0- to 24-week change in Pervasive Developmental Disorders Behavioral Inventory   |

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Table 2 (continued)

| Compound/Dose  | Mechanism of Action | Total n of active arms | Control | Total n subjects | Age range | Trial Duration | Funding/Manufacturer  | Phase | NCT/EUDRACT number | Country | Start date     | Descriptive Results (primary outcome) | Comments   |
|--|---------------------|------------------------|---------|------------------|-----------|----------------|---|-------|--------------------|---------|----------------|---------------------------------------|--|
| Omega 3 fatty acids (Coromega), 1.3 g (1.1 g of DHA + EPA).  |                     | 1                      | Placebo | 57               | 5–8       | 42             | Hugo W. Moser Research Institute at Kennedy Krieger, Inc.               | 2     | NCT01694667        | USA     | September 2012 | Not superior                          | (PDDBI) autism composite scores ( $p = 0.5$ ). There was a significant group by week interaction on the Behavior Assessment System for Children (BASC-2) externalizing problem score, with participants randomized to the treatment group demonstrating worsening scores ( $p = 0.02$ ). Tolerability: no serious AE in either arms. Results in doi: 10.1186/s13229-015-0010-7<br>Efficacy: Not significant changes in Aberrant Behavior Checklist - Hyperactivity Subscale (ABC-H) Score (parent-rated, $ES=0.26$ ; $p = 0.38$ or teacher-rated, $ES=0.18$ , $p = 0.50$ ) from baseline to week 6. Tolerability: no serious AE in either arms. Results in doi: 10.1016/j.jaac.2014.01.018 |
| Omega 3–6 fatty acids, 50 mg/kg, 100 mg/kg, or 150 mg/kg of gamma-linoleic acid (GLA) + eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) |                     | 3                      | Placebo | 72               | 2–6       | 90             | National Center for Complementary and Integrative Health (NCCIH)        | 2     | NCT03550209        | USA     | June 2018      | N/A                                   | Efficacy: No clinical outcome measures included in this trial: Primary endpoints (A) bioavailability, (B) safety and (C) change in IL-1 $\beta$ , IL-2 and IFN $\gamma$ from baseline at 90 days. No serious AE in either arm. Results in doi: 10.1007/s10803-021-05396-9  |
| Oxytocin, 8–80 IU/day  | Hormonal activity   | 1                      | Placebo | 290              | 3–17      | 168            | Institute of Child Health and Human Development (NICHD) Duke University | 2     | NCT01944046        | USA     | August 2014    | Not superior                          | Efficacy: Not significant change in Aberrant Behavior Checklist-Modified Social Withdrawal Subscale ABC-mSW from baseline to week 24 (group difference, $-0.2$ points; 95%CI: $-1.5$ to $1.0$ ; $p = 0.61$ ). Tolerability: 4 (2.7%) and 3 (2.0%) participants discontinued treatment due to AE, in the oxytocin and placebo arms, respectively. Results in doi: 10.1056/NEJMoa2103583   |

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Table 2 (continued)

| Compound/Dose   | Mechanism of Action         | Total n of active arms | Control | Total n subjects | Age range      | Trial Duration | Funding/ Manufacturer   | Phase | NCT/ EUDRACT number | Country | Start date    | Descriptive Results (primary outcome)                      | Comments   |
|---|-----------------------------|------------------------|---------|------------------|----------------|----------------|---|-------|---------------------|---------|---------------|--|--|
| Oxytocin 24IU BID (3 × 0.1 ml [4IU])  |                             | 1                      | Placebo | 54               | 6–12           | 28             | Stanford University   | 2     | NCT01624194         | USA     | June 2012     | Superior   | Primary endpoint: Change From Baseline in Parent Rated Social Responsiveness Scale (SRS) Scores from baseline to week 4 (No ES reported, $p = 0.028$ ).<br>Tolerability: no serious adverse events in either arm.<br>Results in doi: 10.1073/pnas.1705521114   |
| Oxytocin (Syntocinon) 12 IU BID intranasally.   |                             | 1                      | Placebo | 80               | 8–12           | 56             | University Hospital Leuven / KU Leuven  | 31–1  | 2018–000769–35      | Belgium |               | Not superior   | Efficacy: No significant change in parent-reported social responsiveness (No ES reported, $p = 0.63$ ).<br>Tolerability: serious AE in 0% and 10% of participants in oxytocin and placebo arms   |
| Sertraline 2.5 or 5 mg/day  | SSRI                        | 1                      | Placebo | 58               | 24–72 (Months) | 6 months       | Health Resources and Services Administration (HRSA) University of California, Davis               | 2     | NCT02385799         | USA     | April 2015    | Not superior   | Efficacy: No significant (A) Change in Mullen Scales of Early Learning - Expressive Language Raw Score from baseline six-month visit ( $p = 0.55$ ), and (B) Change in Mullen Scales of Early Learning - Combined Age Equivalent Score from baseline visit to six-month visit ( $p = 0.30$ ). No ES reported.<br>Tolerability: serious AE in 3.13% and 0% of participants in sertraline and placebo arms.<br>Results in doi: 10.3389/fpsy.2019.00810 |
| Simvastatin, 0.5–1 mg/kg/day, maximum dose 30 mg/day.   | HMG-CoA reductase inhibitor | 1                      | Placebo | 34               | 5–8            | 112            | Central Manchester University Hospitals NHS Foundation Trust                                      | 2     | 2012–005742–38      | UK      |               | Well tolerated but study not powered to test effectiveness | Autism in young children with neurofibromatosis type 1.<br>Efficacy: Study not powered to test effectiveness.<br>Tolerability: No serious AE leading to discontinuation either arm.<br>Results in: doi 10.1186/s13229-018-0190-z.  |
| Sulforaphane, dose by bodyweight (30–50 lb 45 μmol/day, 50–70 lb 60 μmol/day, 70–90 lb 90 μmol/day, | Antioxidant activity        | 1                      | Placebo | 60               | 3–12           | 252            | University of Massachusetts, Worcester, Congressionally Directed Medical Research Programs, Johns | 31–1  | NCT02561481         | USA     | December 2015 | Not superior   | Efficacy: Change in Ohio Autism Clinical Impressions Scale - Improvement (OACIS-I) Average Score from baseline to weeks 7, 15, 22, 30 and 36 (ES=0.21, 0.10, 0.00, -0.14, and 0.26,  |

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Table 2 (continued)

| Compound/Dose   | Mechanism of Action | Total n of active arms | Control | Total n subjects | Age range | Trial Duration | Funding/Manufacturer                | Phase | NCT/EUDRACT number | Country | Start date | Descriptive Results (primary outcome)       | Comments  |
|---|---------------------|------------------------|---------|------------------|-----------|----------------|-------------------------------------|-------|--------------------|---------|------------|---|---|
| 90–110 lb 105 $\mu\text{mol/day}$ ,<br>110–130 lb 120 $\mu\text{mol/day}$ ) |                     |                        |         |                  |           |                | Hopkins University                  |       |                    |         |            |   | respectively – all with p-values >0.05).<br>Tolerability: serious AE in 0% and 4.35% of participants in sulforaphane and placebo arms.<br>Results in doi: 10.1186/s13229-021-00447-5  |
| Suramin, 20 mg/kg IV single dose  | Antimalarial        | 1                      | Placebo | 10               | 4–17      | 42             | University of California, San Diego | 1  2  | NCT02508259        | USA     | May 2015   | Superior on one of the two primary outcomes | Efficacy: (A) Significant change in Autism Diagnostic Observation Schedule, 2nd Edition (ADOS2) from baseline to week 6 (p = 0.0028), but not in (B) change in Expressive One Word Picture Vocabulary Test (EOWPVT) scores normalized for age from baseline to week 6 (p = 0.32). ES not reported.<br>Tolerability: no serious AE in either arm |

**Table 3**

Retrieved RCTs with positive or negative findings for bipolar disorder, depressive disorders and eating disorders.

| Compound/Dose  | Mechanism of Action  | Total n of active arms | Control   | Total n subjects | Age range | Trial Duration                    | Funding/Manufacturer  | Phase | NCT/EUDRACT number | Country | Start date    | Descriptive Results (primary outcome) | Comments   |
|--|--|------------------------|---|------------------|-----------|-----------------------------------|---|-------|--------------------|---------|---------------|---------------------------------------|--|
| <b>BIPOLAR DISORDER</b>  |  |                        |   |                  |           |                                   |   |       |                    |         |               |                                       |  |
| Inositol 80 mg/kg and Omega-3 Fatty Acids (975 mg eicosapentaenoic acid and 675 mg docosahexaenoic acid) | Alters arachadonic acid metabolism and oxidative reactions   | 3                      | 3 Active comparator arms; Omega-3 + Placebo, Inositol + Placebo and Omega-3 + Inositol. | 69               | 5–12      | 84                                | Massachusetts General Hospital  | 4     | NCT01396486        | USA     | February 2012 | Superior                              | In participants with a DSM-IV diagnosis of a bipolar spectrum disorder (type I, II, or Not Otherwise Specified (NOS)).<br>Efficacy: Subjects randomized to the omega-3 fatty acids plus inositol arm had the largest score decrease at 12 weeks in the Young Mania Rating Scale ( $p < .05$ ) and the Children's Depression Rating Scale ( $p < .05$ ).<br>Tolerability: 1 (5.0%), 1 (5.26%) and 0 serious AE in the omega-3/placebo, placebo/inositol, and omega-3/inositol arm, respectively.<br>Result available in: doi: 10.4088/JCP.14m09267                  |
| Lithium, variable dose   | Inhibition of inositol monophosphatase, adenylyl-cyclase, GMP, glycogen synthase kinase 3, increasing activity of serotonin and acetylcholine; modulator of intracellular signalling cascade | 1                      | Placebo   | 81               | 7–17      | Not specified, minimum 17 months. | Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) | 1–3   | NCT01166425        | USA     | June 2010     | Superior                              | In participants with manic or mixed episodes of bipolar I disorder FDA approved for adolescents aged 12–17; here: 7–17 years.<br>Efficacy: Change from baseline to 8 weeks in the Young Mania Rating Scale (YMRS) score, based on last-observation-carried-forward analysis was significantly larger in the lithium group (5.51 [95% confidence interval: 0.51–10.50]) after adjustment for baseline YMRS score, age group, weight group, gender, and study site ( $p = 0.03$ ).<br>Tolerability: No participants discontinued due to AE. Results in doi: 10.1542/ |

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Table 3 (continued)

| Compound/Dose   | Mechanism of Action  | Total n of active arms | Control   | Total n subjects | Age range | Trial Duration | Funding/Manufacturer                        | Phase | NCT/EUDRACT number          | Country  | Start date    | Descriptive Results (primary outcome)          | Comments   |
|---|--|------------------------|-----------|------------------|-----------|----------------|---|-------|-----------------------------|----------|---------------|--|--|
| <b>DEPRESSIVE DISORDERS</b>                                     |  |                        |           |                  |           |                |   |       |                             |          |               |  |  |
| Agomelatine, 10 and 25 mg/day                                   | Agonist at melatonin receptors and an antagonist at serotonin-2 C (5-HT2C) receptors | 3                      | Placebo   | 484              | 7–18      | 84             | Institut de Recherche International Servier | 3     | 2015–002181–23              | Multiple | February 2016 | 10 mg/day: Not superior<br>25 mg/day: superior | Additional active arm: fluoxetine 10–20 mg/day.<br>Efficacy: 25 mg/day agomelatine resulted in an improvement versus placebo (n = 101) in CDRS-R raw score of 4.22 (95% CI 0.63–7.82; p = 0.040) at 12 weeks, with a similar effect for fluoxetine, establishing assay sensitivity. The overall effect was confirmed in adolescents but not in children.<br>Tolerability: Serious treatment-emergent AE in 6 (5.8%) patients on 10 mg agomelatine, 3 (3.1%) on 25 mg agomelatine, and 7 (0.7%) fluoxetine.<br>Results also in DOI: 10.1016/S2215–0366(21)00390–4 |
| Desvenlafaxine sustained release (DVS SR), 25, 35, or 50 mg/day | Serotonergic and norepinephrergic reuptake inhibitor                                 | 1                      | Placebo   | 363              | 7–17      | 56             | Pfizer                                      | 3     | NCT01371734; 2008–001875–32 | Multiple | August 2011   | Not superior                                   | Tolerability: 2 (1.6%) patients in the desvenlafaxine 25 mg arm reported serious AE. Results available also in doi: 10.1089/cap.2017.0099  |
| Desvenlafaxine sustained release (DVS SR), 25, 35, or 50 mg/day |  | 2                      | Placebo   | 340              | 7–17      | 56             | Pfizer                                      | 3     | NCT01372150                 | Multiple | November 2011 | Not superior                                   | Additional active arm: fluoxetine<br>Tolerability: serious AE in 1.79% and 0% of participants in fluoxetine and placebo arms, respectively.  |
| Duloxetine, dose not specified                                  | Serotonergic and norepinephrergic reuptake inhibitor                                 | 1                      | Placebo   | 149              | 9–17      | 42             | Shionogi                                    | 3     | NCT03315793                 | Japan    | December 2017 | Not superior                                   | Tolerability: no serious AE in either arm.   |
| Ketamine, 0.5 mg/kg   | Glutamate antagonist   | 2                      | Midazolam | 17               | 13–17     | 1              | Yale University                             | 4     | NCT02579928                 | USA      | October 2015  | Superior                                       | Efficacy: Single ketamine infusion significantly reduced depressive symptoms 24 h after infusion compared with<br><i>(continued on next page)</i>  |



Table 3 (continued)

| Compound/Dose                          | Mechanism of Action                                    | Total n of active arms | Control | Total n subjects | Age range | Trial Duration | Funding/Manufacturer | Phase | NCT/EUDRACT number | Country    | Start date    | Descriptive Results (primary outcome) | Comments  |
|--|--|------------------------|---------|------------------|-----------|----------------|----------------------|-------|--------------------|------------|---------------|---------------------------------------|---|
|  |  |                        |         |                  |           |                |                      |       |                    |            |               |                                       | midazolam (MADR score: midazolam, mean=24.13, SD=12.08, 95% CI=18.21, 30.04; ketamine, mean=15.44, SD=10.07, 95% CI=10.51, 20.37; mean difference=-8.69, SD=15.08, 95% CI=-16.72, -0.65, df=15; effect size=0.78). Tolerability: no serious AE in either arm. Results also in doi: 10.1176/appi.ajp.2020.20010018 |
| Levomilnacipran, 10, 20, and 40 mg/day | Norepinephrinergic and serotonergic reuptake inhibitor | 2                      | Placebo | 501              | 7–17      | 56             | Allergan             | 3     | NCT03569475        | USA        | July 2018     | Not superior                          | Additional active arm: fluoxetine<br>Tolerability: Serious treatment-emergent AE in 1 (0.60%) of patients on levomilnacipran and 1 (0.63%) patients on placebo.   |
| Levomilnacipran, 40 mg/day             |  | 2                      | Placebo | 552              | 12–17     | 56             | Forest Laboratories  | 3     | NCT02431806        | USA        | June 2015     | Not superior                          | Additional active arm: fluoxetine<br>Tolerability: Serious treatment-emergent AE in 2 (1.49%) of patients on levomilnacipran 40 mg/day, 0 patients on levomilnacipran 80 mg/day, 4 (2.99%) of patients on fluoxetine 20 mg/day and 0 patients on placebo.   |
| Vilazodone, 5, 10, 20 mg/day           | Serotonergic modulator                                 | 2                      | Placebo | 473              | 7–17      | 56             | Forest Laboratories  | 3     | NCT02372799        | USA-Canada | February 2015 | Not superior                          | Additional active arm: fluoxetine.<br>Tolerability: Serious treatment-emergent AE in 6 (6.19%) of patients on fluoxetine, 0 patients on vilazodone, and 1 (0.54%) of patients on placebo.   |
| Vilazodone, 15 and 30 mg/day           |  | 2                      | Placebo | 529              | 12–17     | 56             | Forest Laboratories  | 3     | NCT01878292        | USA        | July 2013     | Not superior                          | Tolerability: Serious treatment-emergent AE in 3 (1.67%) of patients on vilazodone 30 mg/day, 2 (1.14%) patients on vilazodone 15 mg/day, and 1 (0.58%) of  |

(continued on next page)

Table 3 (continued)

| Compound/Dose                  | Mechanism of Action    | Total n of active arms | Control | Total n subjects | Age range | Trial Duration | Funding/Manufacturer         | Phase | NCT/EUDRACT number          | Country  | Start date    | Descriptive Results (primary outcome)                    | Comments  |
|--------------------------------|------------------------|------------------------|---------|------------------|-----------|----------------|------------------------------|-------|-----------------------------|----------|---------------|--|---|
| Vortioxetine, 10 and 20 mg/day | Serotonergic modulator | 3                      | Placebo | 683              | 7–11      | 84             | H. Lundbeck A/S, Takeda      | 3     | NCT02709655; 2008–005353–38 | Multiple | May 2016      | Not superior   | patients on placebo. Results in doi: 10.1007/s40272–018–0290–4<br>Additional active arm: fluoxetine 20 mg/day. Tolerability: Serious treatment-emergent AE in 1 (0.66%) of patients on vortioxetine 10 mg/day, 2 (1.31%) patients on vortioxetine 20 mg/day, 1 (1.20%) on fluoxetine 20 mg/day, and 3 (1.96%) of patients on placebo. |
| Vortioxetine, 10 and 20 mg/day |                        | 3                      | Placebo | 784              | 12–17     | 56             | H. Lundbeck A/S, Takeda      | 3     | NCT02709746; 2008–005354–20 | Multiple | February 2016 | Not superior   | Additional active arm: fluoxetine 20 mg/day<br>Tolerability: Serious treatment-emergent AE in 4 (2.72%) of patients on vortioxetine 10 mg/day, 7 (4.35%) patients on vortioxetine 20 mg/day, 3 (1.96%) on fluoxetine 20 mg/day, and 1 (0.65%) of patients on placebo. Results in doi: 10.1016/j.jaac.2022.01.004                      |
| <b>EATING DISORDERS</b>        |                        |                        |         |                  |           |                |                              |       |                             |          |               |  |   |
| Somatropin, 0.05 mg / kg / day | Growth hormone         | 1                      | Placebo | 15               | 8–16,9    | 2 years        | Robert Debré Hospital, Paris | 2–3   | NCT01626833; 2010–018560–16 | France   | March 2013    | Superior (greater increase in height than placebo group) | In anorexia nervosa. Efficacy: Increase in height at 6 months p = 0.045 (ES not reported). Tolerability: No participants discontinued due to AE. Results in DOI: 10.1210/clinem/dgab203   |

**Table 4**

Retrieved RCTs with positive or negative findings for intellectual and developmental disability, obsessive-compulsive disorder, schizophrenia, Tourette's syndrome, and PTSD.

| Drug/Dose  | Mechanism of Action   | Total n of active arms | Control | Total n subjects | Age range | Trial Duration | Funding/Manufacturer          | Phase | NCT/EUDRACT number          | Country  | Start date    | Descriptive Results (primary outcome)  | Comments  |
|--|---|------------------------|---------|------------------|-----------|----------------|-------------------------------|-------|-----------------------------|----------|---------------|--|---|
| <b>INTELLECTUAL and DEVELOPMENTAL DISABILITY</b>   |   |                        |         |                  |           |                |                               |       |                             |          |               |  |   |
| AFQ056, 25, 50 or 100 mg BID   | mGluR5 negative modulator   | 3                      | Placebo | 139              | 12–17     | 84             | Novartis Pharmaceuticals      | 2     | NCT01357239; 2010–022638–96 | Multiple | May 2011      | Not superior   | In patients with Fragile X syndrome. Efficacy: Results available, but no calculation of statistical significance. Tolerability: (adolescent group): 1 (3.2%) participant in the mavoglurant group and 1(2.3%) in the placebo group experienced serious AE. Results in doi: 10.1126/scitranslmed.aab4109   |
| Cannabidiol (ZYN002) transdermal gel, 250 mg/day if bodyweight < 35 kg, otherwise 500 mg/day | Binds to CB1 and CB2 receptors of the endocannabinoid system; activates 5-HT1A serotonergic and TRPV1–2 vanilloid receptors | 1                      | Placebo | 212              | 3–17      | 84             | Zynerba Pharmaceuticals, Inc. | 1–3   | NCT03614663                 | Multiple | June 2018     | Not superior for the full analysis subset, but superior for the ad hoc analysis subset.            | In patients with Fragile X syndrome. Efficacy: Change at week 12 in the Aberrant Behavior Checklist-Community Fragile X Factor Structure (ABC-C FXS) Social Avoidance Subscale - Ad Hoc Analysis, $p = 0.02$ . Significance was not demonstrated in the other primary endpoint, Aberrant Behavior Checklist-Community Fragile X Factor Structure (ABC-C FXS) Social Avoidance Subscale - Full Analysis Set. Tolerability: no serious AE in either arm.                              |
| Carbetocin, FE 992097 (LV-101), 3.2 or 9.6 mg three times a day intranasally.                | Long-acting synthetic oxytocin analogue   | 2                      | Placebo | 130              | 7–18      | 56             | Levo Therapeutics, Inc.       | 3     | NCT03649477                 | Multiple | November 2018 | Superior at 3.2 mg TDS for hyperphagia endpoint only. 9.6 mg TDS not superior for either endpoint. | In patients with Prader-Willi syndrome. Efficacy: Change in Hyperphagia Questionnaire for Clinical Trials (HQ-CT) at eight weeks demonstrated significance for Carbetocin 3.2 mg TDS, $p = 0.0162$ , Mean difference – 3.136 (2-sided 95% CI –5.685 to –0.586). Significance not demonstrated for the higher dose or for the other primary endpoint (Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) from baseline at 8 weeks). Tolerability: no serious AE across arms. |
| Carbetocin, FE 992097, dose not specified  |   | 1                      | Placebo | 38               | 10–18     | 15             | Ferring Pharmaceuticals       | 2     | NCT01968187                 | USA      | January 2014  | Superior   | In patients with Prader-Willi syndrome. Efficacy: Change in total hyperphagia score at day 15   |

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Table 4 (continued)

| Drug/Dose  | Mechanism of Action                      | Total n of active arms | Control                               | Total n subjects | Age range | Trial Duration | Funding/Manufacturer                                      | Phase | NCT/EUDRACT number          | Country     | Start date    | Descriptive Results (primary outcome) | Comments  |
|--|--|------------------------|---------------------------------------|------------------|-----------|----------------|---|-------|-----------------------------|-------------|---------------|---------------------------------------|---|
|  |  |                        |                                       |                  |           |                |   |       |                             |             |               |                                       | measured by the Hyperphagia for Prader-Willi Syndrome Questionnaire was – 15.6 versus placebo – 8.9; P = 0.029). Tolerability: no serious AE in either arm. Results in doi: 10.1172/jci.insight.98333   |
| Dextromethorphan, 5 mg/kg/day  | NMDA receptor antagonist                 | 1                      | Placebo                               | 57               | 1–10      | 3 months       | Hugo W. Moser Research Institute at Kennedy Krieger, Inc. | 2     | NCT01520363                 | USA         | March 2012    | Not superior                          | In patients with Rett syndrome who are MECP2 mutation positive. Tolerability: no serious AE across arms.  |
| Everolimus, 5–10 ng/ml   | Kinase inhibitor                         | 1                      | Placebo                               | 60               | 4–15      | 12 months      | Erasmus Medical Center Utrecht University                 | 2 3   | NCT01730209                 | Netherlands | November 2012 | Not superior                          | In tuberous sclerosis. Primary endpoint was cognitive ability measures as IQ. Trial also looked at changes in autistic features. Tolerability: 2 (13.3%) patients on everolimus and 2 (11.7%) on placebo discontinued due to AEs. Results in doi: 10.1212/WNL.0000000000007749  |
| Ganaxolone (GNX, also known as GNX OS), 3–12 mg/kg, maximum 1500 mg/day. | Positive allosteric GABA-A modulation    | 2                      | Placebo, crossover trial.             | 59               | 6–17      | 98             | Marinus Pharmaceuticals                                   | 2     | NCT01725152; 2014-000251-89 | Multiple    | November 2012 | Not superior                          | In patients with Fragile X syndrome for the treatment of anxiety and attention. Primary endpoint: improvement in Clinical Global Impression (CGI-I). Tolerability: no serious AE were reported. Results available in doi: 10.1186/s11689-017-9207-8   |
| Idursulfase, 10 mg/month intrathecally                                   | Iduronate-2-sulfatase enzyme replacement | 1                      | Standard of care (weekly IV Elaprase) | 52               | up to 18  | 364            | Shire, Takeda   | 1-3   | NCT02055118                 | Multiple    | March 2014    | Not superior                          | In patients with Hunter Syndrome and early cognitive impairment. Tolerability: serious E in 12 (36.36%) n active treatment and 2 (13.3%) on control treatment. Results available in DOI: 10.1016/j.yngme.2022.07.017 and DOI: 10.1016/j.yngme.2022.07.016   |
| Lovastatin, 10–40 mg/day   | HMG-CoA reductase inhibitor              | 1                      | Placebo                               | 30               | 10–17     | 140            | University of California, Davis                           | 4     | NCT02642653                 | USA         | January 2016  | Not superior                          | In patients with Fragile X syndrome. Primary endpoints are expressive language sample composite scores in the home at baseline and 20 weeks. Both arms also received the behavioural treatment, Parent Implemented Language Intervention (PILI). Unclear whether statistical analysis performed, but publication states there was no difference between arms. Tolerability: 2 (12.5%) on active treatment discontinued due to AE. |

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Table 4 (continued)

| Drug/Dose   | Mechanism of Action                        | Total n of active arms | Control   | Total n subjects | Age range          | Trial Duration | Funding/Manufacturer        | Phase | NCT/EUDRACT number | Country | Start date   | Descriptive Results (primary outcome)  | Comments  |
|---|--|------------------------|---|------------------|--------------------|----------------|-----------------------------|-------|--------------------|---------|--------------|--|---|
| Oxytocin (Syntocinon) 16 IU/day intranasally                              | Hormonal activity                          | 1                      | Placebo   | 23               | 5–18               | 56             | Montefiore Medical Center   | 2     | NCT02629991        | USA     | October 2015 | Superior for Hyperphagia Questionnaire (HQ)- Drive Factor Score. No superiority for other primary endpoints. | No serious AE in either group. Results also in doi: 10.1186/s11689-020-09315-4. In patients with Prader-Willi syndrome. Four primary endpoints, 1. Hyperphagia Questionnaire (HQ)- Total Score, 2. Hyperphagia Questionnaire (HQ)- Behavior Factor Score, 3. Hyperphagia Questionnaire (HQ)- Drive Factor Score, 4. Hyperphagia Questionnaire (HQ)- Severity Factor Score<br>Efficacy demonstrated only for HQ- Drive Factor Score, p = 0.027<br>Tolerability: No serious AE in either group. |
| Oxytocin (Syntocinon) 4 IU/day intranasally                               |  | 1                      | Placebo   | 15               | 1 Week to 6 Months | 5              | University of Florida       | 31-1  | NCT03245762        | USA     | August 2017  | Not superior   | In patients with Prader-Willi syndrome. Primary endpoint is Suck and Swallow Competency in Infants/Children With PWS Who Are in Nutritional Phase 1a. Tolerability: No serious AE in either group.  |
| Thyroxine 25 mcg/day + Folinic acid 5 mg/day                              | Hormone                                    | 3                      | Three comparator arms: 1. Placebo, 2. Thyroxine + Placebo, 3. Folinic acid + Placebo. | 175              | 6–18 (Months)      | 12 months      | Institut Jerome Lejeune     | 3     | NCT01576705        | France  | April 2012   | Not superior   | In patients with Down Syndrome. Efficacy: Primary outcome is Griffiths Mental Development Scale score at 12 months: Difference (Thyroxine+folinic acid vs. placebo) 1.24; p = 0.38. Tolerability: 1 (2.33%) serious AE in the thyroxin+folinic acid arm, none in the other arms. Results available in doi: 10.1038/s41436-019-0597-8  |
| <b>OBSESSIVE COMPULSIVE DISORDER</b><br>D-Cycloserine, dose not specified | GABA transaminase inhibitor and antibiotic | 2                      | Placebo   | 142              | 7–17               | 70             | University of South Florida | 3     | NCT01411774        | USA     | June 2011    | Not superior   | Additional active arm: CBT-D-Cycloserine to Augment CBT. Efficacy: ES 0.31–0.47<br>Tolerability: no (serious) AE<br>Results also in 10.1016/j.biopsych.2010.07.015  |
| Fluvoxamine 25–150 mg/day   | SSRI                                       | 1                      | Placebo   | 38               | 6–18               | 70             | AbbVie                      | 3     | NCT01933919        | Japan   | August 2013  | Superior   | Approved for use in 8 years and older, trial recruits from age 6–18. Efficacy: Change in CY-YBOCS at week 10: Mean difference – 4.3; p = 0.044<br>Tolerability: 1 (6.67%) participant with serious AE in the second phase, placebo/fluvoxamine arm,   |

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Table 4 (continued)

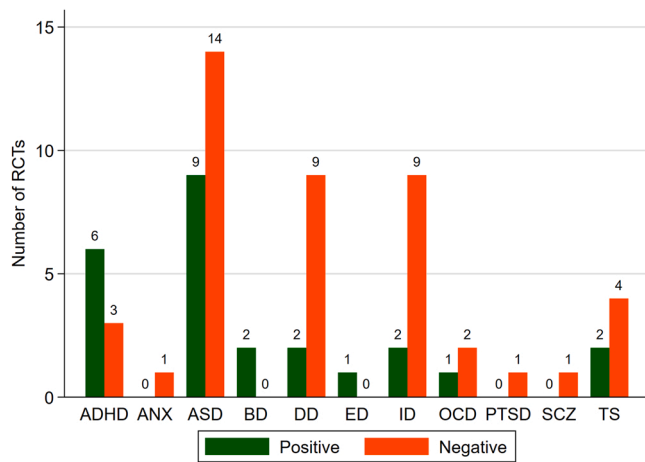
| Drug/Dose   | Mechanism of Action   | Total n of active arms | Control | Total n subjects | Age range | Trial Duration | Funding/Manufacturer                           | Phase | NCT/EUDRACT number          | Country       | Start date     | Descriptive Results (primary outcome)               | Comments   |
|---|---|------------------------|---------|------------------|-----------|----------------|--|-------|-----------------------------|---------------|----------------|---|--|
| Gamunex Intravenous Immunoglobulin, 2.0 gm/kg                               | Immunoglobulin  | 1                      | Placebo | 48               | 4–13      | 42             | National Institute of Mental Health (NIMH)     | 3     | NCT01281969                 | USA           | January 2011   | Not superior  | no other participants with serious AE in the other arms<br>For PANDAS<br>Efficacy: Change in CY-BOCS at week 6: Mean difference – 1.97; p = 0.044<br>Tolerability: no serious AE in either arm<br>Result also in<br>DOI: 10.1016/j.jaac.2016.06.017<br>Tolerability: no serious AE in either arm   |
| N-acetylcysteine, 900 mg up to 3 times/day                                  | Prodrug to L-cysteine; increases the concentration of glutathione. Prevention of glutamate overactivity, oxidative stress and neuronal damage | 1                      | Placebo | 11               | 8–17      | 84             | Yale University                                | 2     | NCT01172275                 | USA           | July 2012      | Statistical analysis not reported                   |  |
| <b>PTSD</b><br>Sertraline   | SSRI  | 2                      | Placebo |                  | 6–17      | 10             | Pfizer   | 3     | 2014-004162-17              | USA           | March 2015     | Not superior  | Primary efficacy outcome: UCLA PTSD-I scores: Not significant (p = 0.212)  |
| <b>SCHIZOPHRENIA</b><br>Asenapine, 2.5 or 5 mg BID                          | Dopaminergic, serotonergic, and norepinephrinergic antagonist   | 2                      | Placebo | 306              | 12–17     | 56 days        | Merck Sharp & Dohme Corp                       | 3     | NCT01190254; 2009-017971-10 | Not specified | September 2010 | Not superior  | Efficacy: Mean difference in PANSS total at week 26<br>2.5 mg BID – 4.8; p = 0.07<br>5 mg BID – 5.6; p = 0.064<br>Tolerability: serious AE in 3 (3.06%), 3 (2.83%) and 3 (2.94%) of participants on asenapine 2.5 mg/day, 5 mg/day, and placebo, respectively<br>Results also in doi: 10.1089/cap.2015.0027  |
| <b>TOURETTE'S SYNDROME</b><br>AZD5213, 0.5 or 2 mg, frequency not specified | Selective H3R antagonist/inverse agonist  | 2                      | Placebo | 29               | 12–17     | 6 months       | AstraZeneca                                    | 2     | NCT01904773                 | USA           | August 2013    | Superior at 2 mg dose, not superior at 0.5 mg dose. | Efficacy: Change in YGTSS-TTS at week 3 vs. placebo<br>0.5 mg: p = 0.12<br>2 mg: p = 0.0087<br>Tolerability: part 1: 0, 1 (4.17%) and 0 participants in the AZD5213 0.5 mg/day, 2 mg/day, and placebo, respectively, had serious AE; part 2: 0, 0, and 1 (4.76%) in the in the AZD5213 0.5 mg/day, 2 mg/day, and placebo, respectively, had serious AE |
| Deutetrabenazine (TEV-50717), 36 or 48 mg/day                               | Reversible VMAT2 inhibitor  | 2                      | Placebo | 158              | 6–16      | 63             | Teva Branded Pharmaceutical Products R&D, Inc. | 3     | NCT03571256; 2017-002976-24 | Multiple      | May 2018       | Not superior  | Efficacy: Change in YGTSS-TTS at week 8 vs. placebo<br>36 mg/d: ES 0.14<br>48 mg/d: ES – 0.11  |

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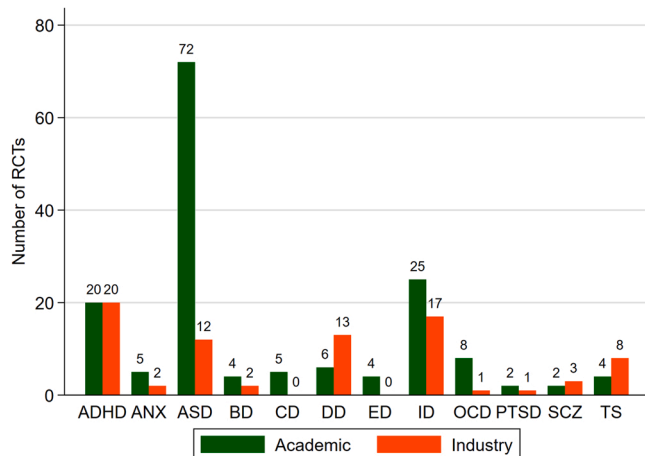
Table 4 (continued)

| Drug/Dose  | Mechanism of Action                    | Total n of active arms | Control | Total n subjects | Age range | Trial Duration | Funding/Manufacturer                           | Phase | NCT/EUDRACT number          | Country  | Start date    | Descriptive Results (primary outcome) | Comments   |
|--|--|------------------------|---------|------------------|-----------|----------------|--|-------|-----------------------------|----------|---------------|---------------------------------------|--|
| Deutetrabenazine (TEV-50717), up to 48 mg/day  |  | 1                      | Placebo | 119              | 6–16      | 98             | Teva Branded Pharmaceutical Products R&D, Inc. | 1–3   | NCT03452943; 2016-000622–19 | Multiple | February 2018 | Not superior                          | Tolerability: 1 (1.92%), 0 and 0 participants in the TEV50717 high-dose, low-dose, and placebo, respectively, had serious AE<br>Results in doi: 10.1001/amanetworkopen.2021.29397<br>Efficacy: Change in YGTSS-TTS at week 12 vs. placebo 48 mg/d: ES – 0.07<br>Tolerability: no serious AE in either arm<br>Results in doi: 10.1001/amanetworkopen.2021.28204 |
| Ecopipam (SCH 39166, also known as PSYRX101), dose not specified   | Selective dopamine D1 receptor blocker | 1                      | Placebo | 40               | 7–17      | 30             | Psyadon Pharma                                 | 2     | NCT02102698                 | USA      | March 2014    | Superior                              | Efficacy: Change in YGTSS-TTS at day 30 vs. placebo: Mean difference – 3.2; p = 0.033<br>Tolerability: no serious AE in either arm<br>Results available in doi: 10.1002/mds.27457  |
| Valbenazine (Ingrezza, also called NBI-98854) 20–60 mg/day if bodyweight < 50 kg, 40–80 mg/day if bodyweight ≥ 50 kg | Presynaptic VMAT2 inhibitor            | 1                      | Placebo | 127              | 6–17      | 84             | Neurocrine Biosciences                         | 2     | NCT03325010                 | Multiple | October 2017  | Not superior                          | Efficacy: Change in YGTSS-TTS at week 12 vs. placebo: Mean difference – 2.1; p = 0.18<br>Tolerability: 1 (1.61%) and 0 participants with serious AE in the placebo and valbenazine arm, respectively   |
| Valbenazine (Ingrezza, also called NBI-98854) at one of two doses (not further specified)                            |  | 2                      | Placebo | 98               | 6–17      | 42             | Neurocrine Biosciences                         | 2     | NCT02679079                 | USA      | March 2016    | Not superior                          | Efficacy: Change in YGTSS-TTS at week 6 vs. placebo:<br>Low dose: Mean difference – 0.3; p = 0.89<br>High dose: Mean difference 1.5; p = 0.47<br>Tolerability: 1 (3.13%), 0 and 0 participants with serious AE in the placebo, NBI 98854 low-dose, and high dose arm, respectively   |

Legend: AE=Adverse event; CY-BOCS=Children's Yale-Brown Obsessive Compulsive Scale; D=Dopamine; ES=Effect size (e.g. Cohen's d); H=Histamine; VMAT2 =Vesicular monoamine transporter-2; YGTSS-TTS=Yale Global Tic Severity Scale-Total Tic Score. PTSD: post traumatic stress disorder



**Fig. 1.** Summary of positive and negative RCTs grouped by disorder. Legend: ADHD=Attention-deficit hyperactivity disorder; ANX=Anxiety disorders (other than OCD); ASD=Autism-spectrum disorders; BD=Bipolar disorder; DD=Depressive disorders; ED=Eating disorders; ID=Intellectual disability; OCD=Obsessive-compulsive disorder; RCT=Randomized controlled trial; SCZ=Schizophrenia; TS=Tourette's Syndrome.



**Fig. 2.** Summary of sponsorship of RCTs grouped by disorder. Legend: ADHD=Attention-deficit hyperactivity disorder; ANX=Anxiety disorders (other than OCD); ASD=Autism-spectrum disorders; BD=Bipolar disorder; CD=Conduct disorder (and related disorders); DD=Depressive disorders; ED=Eating disorders; ID=Intellectual disability; OCD=Obsessive-compulsive disorder; RCT=Randomized controlled trial; SCZ=Schizophrenia; TS=Tourette's Syndrome.

guanfacine XR versus placebo (54.2% vs. 31.6%) showed investigator-rated CGI-improvement (CGI-I) scores  $\leq 2$  (much or very much improved). Results from the other RCTs were not available.

### 3.3. Autism spectrum disorder (ASD)

We found 84 RCTs. About 86% were sponsored by universities/hospitals/NIMH, and the rest (14%) were funded by drug companies. Among RCTs of pharmaceutical agents ( $n = 70$ ), 81% and 19% were sponsored by university/hospitals and pharmaceutical companies, respectively. Thirty-one mechanisms of action were assessed, including 41 compounds. Mechanisms of action of the compounds assessed in RCTs in autism-spectrum disorders included:

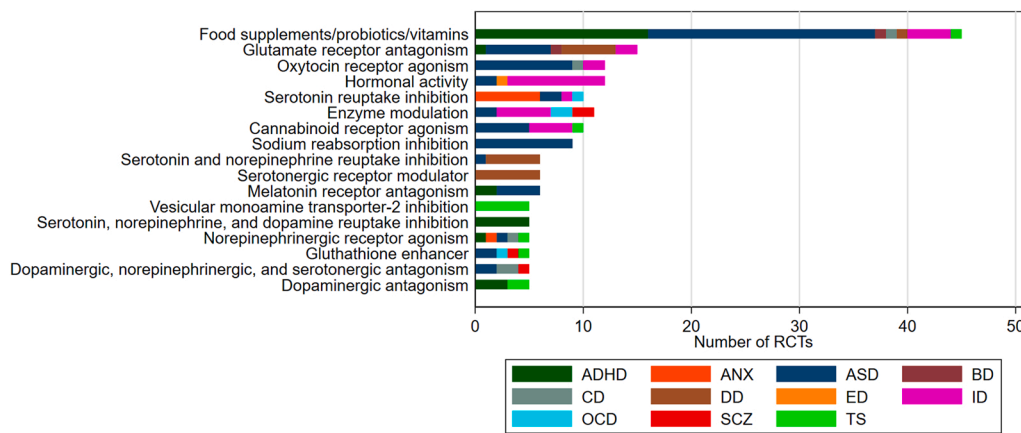
1. Serotonin and norepinephrine reuptake inhibition: amitriptyline ( $n = 1$ )

2. Selective serotonin reuptake inhibition: sertraline ( $n = 2$ )
3. Histaminergic, noradrenergic, and serotonergic receptor antagonism: mirtazapine ( $n = 1$ )
4. Dopaminergic, noradrenergic and serotonergic receptor antagonism (lurasidone,  $n = 1$ ; risperidone,  $n = 1$  - although risperidone is approved by several regulatory bodies for irritability in ASD, here it was tested for ASD defining symptoms)
5. Dopaminergic partial agonism and serotonergic antagonism: cariprazine ( $n = 1$ )
6. Dopaminergic receptor partial agonism: brexpiprazole ( $n = 1$ )
7. Dopaminergic and serotonergic receptor antagonism: olanzapine (which has also muscarinic action) (precision olfactory delivery,  $n = 1$ )
8. Selective GABA-B receptor agonism: arbaclofen ( $n = 2$ )
9. Partial agonist at the glycine NMDA co-agonist site and anti-biotic: D-cycloserine ( $n = 1$ )
10. Norepinephrine (alpha-2) receptor agonism: guanfacine XR ( $n = 1$ )
11. Glutamate receptor antagonism: memantine ( $n = 5$ )
12. Acetylcholinesterase inhibition: donepezil ( $n = 1$ ), given with choline supplements
13. Inhibition of the reabsorption of chloride and sodium by the kidneys and in the brain: bumetanide ( $n = 9$ )
14. Cannabinoid receptor agonism, binding to CB1 and CB2 receptors of the endocannabinoid system: cannabidiol ( $n = 5$ )
15. Activation of the receptors V1a, V1b, and V2: vasopressin ( $n = 2$ )
16. Oxytocin receptor agonism: oxytocin ( $n = 9$ )
17. Neuroactive microbial metabolite (NMMs) removal: AB-2004 ( $n = 1$ )
18. Enhancement of protein digestion: CM-AT ( $n = 1$ )
19. Kinase inhibition: everolimus ( $n = 1$ )
20. Mediation of the effects of growth hormone: Insulin-like growth factor (IGF)-1 ( $n = 1$ )
21. Combination of an NMDA receptor antagonism and agonism of  $\alpha$ -adrenergic receptors: ketamine plus dexmedetomidine ( $n = 1$ )
22. Inhibition of inositol monophosphatase, adenylyl-cyclase, GMP, glycogen synthase kinase 3, increasing activity of serotonin and acetylcholine; modulation of intracellular signalling cascade (lithium carbonate,  $n = 1$ )
23. Inhibition of the mitochondrial respiratory chain; activation of the AMP-activated protein kinase (metformin,  $n = 1$ )
24. Glutathione enhancement (N-acetylcysteine,  $n = 2$ )
25. Serotonergic (2a) receptor inverse agonism and antagonism (pimavanserin,  $n = 1$ )
26. Hormonal activity (growth hormone,  $n = 1$ )
27. Melatonin receptor agonism (melatonin,  $n = 4$ ; of note, an ER formulation of melatonin is approved in some European countries for sleep disorders associated with ASD or ADHD)
28. TTX-sensitive sodium channel inhibition (riluzole,  $n = 1$ )
29. Enzyme modulation - 3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibition (simvastatin,  $n = 1$ )
30. P2 and ryanodine receptor antagonism (suramin,  $n = 1$ )
31. Glycogen synthase kinase 3 inhibition (tideglusib,  $n = 1$ )

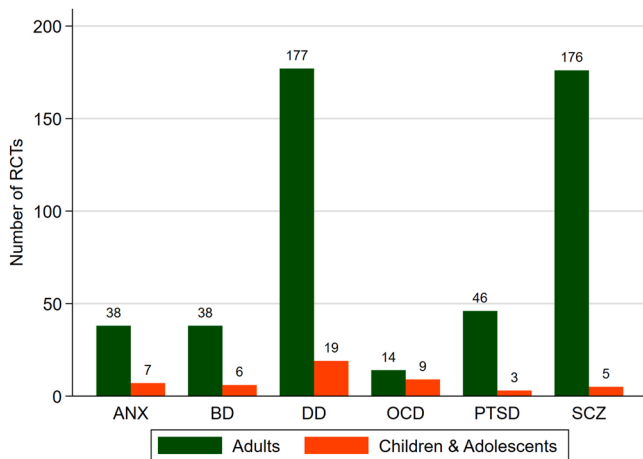
Other RCTs tested probiotics ( $n = 1$ ), ferrous sulfate ( $n = 1$ ), folic acid ( $n = 5$ ), methylcobalamin ( $n = 1$ ), microbiota transfer therapy ( $n = 1$ ), omega-3 fatty acids ( $n = 6$ ), essential oils ( $n = 1$ ), sulforaphane ( $n = 1$ ), vitamin B6 ( $n = 1$ ), vitamin D3 ( $n = 1$ ), and mix of diet components ( $n = 2$ ).

Regarding compounds for which results were available, in one RCT (NCT01078714), bumetanide was superior to placebo for the primary outcome [Childhood Autism Rating Scale (CARS) ( $p = 0.004$ )]. Of note, in another RCT (2013-003259-39), bumetanide was superior to placebo in the secondary outcomes (Social Responsiveness Scale - SRS, CGI-I  $p = 0.0043$ , ES not reported) but not in the primary outcome (CARS). Similarly, in another RCT (2014-001560-35), bumetanide was not





**Fig. 3.** Summary of modes of action, overall and grouped by disorder. Notes: MoAs only shown if investigated in  $\geq 5$  RCTs. Legend: ADHD=Attention-deficit hyperactivity disorder; ANX=Anxiety disorders (other than OCD); ASD=Autism-spectrum disorders; BD=Bipolar disorder; CD=Conduct disorder (and related disorders); DD=Depressive disorders; ED=Eating disorders; ID=Intellectual disability; OCD=Obsessive-compulsive disorder; RCT= Randomized controlled trial; SCZ=Schizophrenia; TS=Tourette's Syndrome.



**Fig. 4.** Summary of RCTs in children and adolescents compared to similar conditions in adults. Notes: Data on the number of RCTs in adults from Correll et al. (2023). Legend: ANX=Anxiety disorders (other than OCD); BD=Bipolar disorder; DD=Depressive disorders; OCD=Obsessive-compulsive disorder; RCT= Randomized controlled trial; SCZ=Schizophrenia.

superior to placebo in the primary outcome (SRS). Finally, another RCT of bumetanide was terminated as the 6-month efficacy analysis on the primary outcome (CARS-2 scores) showed no separation from placebo. D-cycloserine was not superior to placebo at the first endpoint (11 weeks) in the primary outcome (SRS) but it separated significantly from placebo at the 22-week analysis ( $p = 0.048$ ) on the SRS. Suramin was significantly better than placebo in one of the two primary outcomes (Autism Diagnostic Observation Schedule;  $p = 0.0028$  - ES not reported) but not on the other primary outcome (expressive language).

In one RCT (NCT01372449), memantine was not superior to placebo in the primary outcome (adaptive behavior, measured with the Vineland Adaptive Behavior scale). In a withdrawal RCT, memantine did not significantly separate from placebo in any outcome, including the primary one: Proportion of Patients Meeting the Criterion for Loss of Therapeutic Response. Oxytocin was not superior to placebo in two RCTs (NCT01944046 and 2018-000769-35) in any of the outcomes. In another RCT (NCT01624194), oxytocin was superior to placebo on the Total SRS score (primary outcome;  $p = 0.027$ ) and was well tolerated. In terms of non-core symptoms of ASD, in one RCT, guanfacine XR was found better than placebo for the symptom “hyperactivity” in ASD, measured with the Aberrant Behavior Checklist Hyperactivity Subscale (rather than a formal diagnosis of ADHD for which it is approved).

Four other compounds were found not significantly different from placebo on any outcome: sertraline on expressive language scores,

adaptive behavior, anxiety sensory processing, and CGI-I; everolimus on IQ, autistic symptoms, motor skills, sleep, behavioral/emotional problems and quality of life; mirtazapine on anxiety; and lurasidone on irritability. Metformin was tested for the management of overweight/obesity induced by dopamine and serotonin-dopamine antagonist medications in young people with ASD and was superior to placebo ( $p = 0.003$ ). Melatonin was superior to placebo for sleep onset latency in one RCT ( $p < 0.0001$  in the double-blind treatment phase).

Among the non-pharmaceutical agents, folic acid (for ASD core symptoms) and methylcobalamin (on the CGI-I), were superior to placebo in single RCTs. Omega-3 fatty acids (2 RCTs with reported results) and sulforaphane (1 RCT) were not superior to placebo.

### 3.4. Bipolar disorder

We found six RCTs, four (67%) sponsored by hospitals/university and two (33%) funded by pharmaceutical companies. Five RCTs included pharmaceutical agents, assessing 6 modes of action, and including 6 compounds. Mechanisms of action of the compounds assessed in RCTs in bipolar disorder included:

1. Glutamate channel blockade (carbamazepine,  $n = 1$ )
2. Dopaminergic partial agonism and serotonergic antagonism (cariprazine,  $n = 1$ )
3. Inhibition of inositol monophosphatase, adenylyl-cyclase, guanosine monophosphate (GMP), glycogen synthase kinase 3, increasing activity of serotonin and acetylcholine; modulator of intracellular signalling cascade (lithium,  $n = 1$ ; note: lithium has FDA regulatory approval for adolescents aged 12–17 years; here it was tested in children aged 7–17 years),
4. Glutamate receptor antagonism (memantine,  $n = 1$ )
5. Dopaminergic and serotonergic antagonism (perospirone,  $n = 1$ ) given with lithium

Another RCT tested inositol plus omega-3 free fatty acids.

All RCTs, except that for perospirone + lithium, were focused on treating manic/mixed symptoms. Results were reported for the RCT of lithium ( $n = 53$ ), which was superior to placebo ( $n = 28$ ) on the Young Mania Rating Scale, ES: 0.53 (0.06–0.99) and generally well tolerated, and for the pilot RCT of inositol plus omega-3 fatty acids, which was superior to inositol plus placebo or omega-3 fatty acids plus placebo (ES not reported) and well tolerated.

### 3.5. Conduct disorder/oppositional defiant disorder/disruptive mood dysregulation disorder/intermittent explosive disorder

We found five RCTs, all sponsored by universities/hospitals. Four modes of action were assessed, including four compounds. Mechanisms

of action of the compounds assessed in RCTs in these disorders included:

1. Dopaminergic, norepinephrine, and serotonergic antagonism (risperidone,  $n = 2$ ; note: risperidone is approved in isolated European countries but not across Europe through European Medicine Agency (EMA) approval or in the US for conduct disorder)
2. Oxytocin receptor agonism (oxytocin,  $n = 1$ )
3. Norepinephrine (alpha-2) receptor agonism (guanfacine XR,  $n = 1$ )

Another RCT tested omega-3 fatty acids.

Results were not available from any of these RCTs.

### 3.6. Depressive disorders

Nineteen RCTs, including one testing a diet compound, were retained. Overall, about 68% of the RCTs (72% of those testing pharmacological compounds) were funded by drug companies, and 32% sponsored by universities/hospitals. Six modes of action were assessed, including 10 compounds. Mechanisms of action of the compounds assessed in RCTs in depressive disorders include:

1. Serotonergic and norepinephrine reuptake inhibition (desvenlafaxine,  $n = 2$ ; duloxetine,  $n = 1$ ; levomilnacipran,  $n = 2$ )
2. Norepinephrine and dopamine reuptake inhibition (bupropion,  $n = 1$ )
3. Serotonergic receptor modulation (vilazodone,  $n = 2$ ; vortioxetine,  $n = 4$ )
4. Glutamate receptor antagonism (esketamine,  $n = 1$ ; ketamine,  $n = 4$ )
5. Melatonin receptor agonism and serotonergic (2C) receptor antagonism (agomelatine,  $n = 1$ )

Another RCT tested omega-3 fatty acids.

In one proof-of-concept cross-over RCT ( $n = 17$  participants, 16 of which received both treatments) (NCT02579928, Dwyer et al., 2021), a single ketamine infusion significantly reduced depressive symptoms after 24 h compared to midazolam (ES: 0.78, 95% CI not reported), measured on the Montgomery-Åsberg Depression Rating Scale (MADRS) (primary outcome) and improvements remained 14 days after treatment, but no significant differences were found on the Children's Depression Rating Scale-Revised at days 1 and 24. Of note, unblinding for ketamine was 100%. Although ketamine was associated with transient, self-limited dissociative symptoms, there were no serious adverse events. It should be noted that the study was not powered to detect rare events.

Agomelatine 25 mg (but not 10 mg/day) was statistically superior to placebo (ES: 0.29, 95% CI not reported) and comparable to fluoxetine (ES: 0.26 95% CI not reported) in the whole group of children and adolescents. Findings were similar in the adolescent subgroup (ES: agomelatine: 0.36; fluoxetine: 0.27, 95% CI not reported) but not in children; however it should be noted that the study was underpowered in children. Overall, agomelatine was well tolerated.

Non-significant findings were reported regarding the primary outcome CDRS-R total scores for desvenlafaxine ( $n = 2$ ), duloxetine ( $n = 1$ ), levomilnacipran ( $n = 2$ ), vilazodone ( $n = 2$ ) and vortioxetine ( $n = 2$ ) (only CDRS-R reported).

### 3.7. Eating disorders

Four RCTs were retained, all sponsored by universities/hospitals. Four mechanisms of action were assessed, including 4 different compounds. Mechanisms of action of the compounds assessed in RCTs in eating disorders included:

1. Dopaminergic and serotonergic partial agonism and antagonism (aripiprazole,  $n = 1$ )
2. Partial agonist at the glycine NMDA co-agonist site and antibiotic (D-cycloserine,  $n = 1$ )
3. Steroid hormone (megestrol acetate,  $n = 1$ )
4. Hormonal activity (somatropin,  $n = 1$ )

All these RCTs recruited participants with anorexia nervosa, except for the RCT testing D-cycloserine that focused on feeding disorders. The proof-of-concept RCT on somatropin showed that the percentage of patients with a height velocity  $> 5$  cm/year during the study period was greater in the active compared to the placebo group (100% vs. 50%,  $p = 0.05$ ). Results were not available for the other RCTs.

### 3.8. Intellectual and developmental disability (IDD)

The vast majority of identified trials (49/41) in this section pertain to genetic syndromes associated with IDD, even though the presence of IDD was not always documented in the retrieved RCTs. Nonetheless, we have reported RCTs as they may provide interesting etiopathophysiology-based interventions.

Forty-one RCTs, including 4 RCTs of dietary supplements, were found, 60% of which were sponsored by university/hospitals/public bodies and 40% by drug companies (55% and 45%, respectively for pharmacological compounds).

Eighteen modes of action were assessed, including 28 compounds. Mechanisms of action of the compounds assessed in RCTs in intellectual and developmental disability included:

1. Glutamate receptor antagonism (RO4917523,  $n = 1$ ; ketamine,  $n = 1$ )
2. Glutamate receptor negative allosteric modulation (AFQ056,  $n = 2$ )
3. GABA receptor agonism (arbaclofen,  $n = 1$ ; ganaxolone,  $n = 1$ )
4. Norepinephrine transport inhibition (atomoxetine,  $n = 2$ )
5. Inverse agonist/negative allosteric modulation of  $\alpha_5$  subunit-containing GABA (basmisanil,  $n = 1$ )
6. Sigma-1 receptor agonism (blarcamesine,  $n = 1$ )
7. Cannabinoid receptor agonism (cannabidiol,  $n = 4$ )
8. Oxytocin receptor agonism (carbetocin [synthetic oxytocin analogue],  $n = 2$ )
9. Neurotrophic peptide (cerebrolysin,  $n = 1$ )
10. Enzyme modulation (recombinant iduronate 2-sulphatase [IDS] enzyme,  $n = 1$ ; HMG-CoA reductase inhibitor: lovastatin,  $n = 1$ ; phosphodiesterase-4D inhibitor,  $n = 1$ ; mTOR inhibitor: everolimus,  $n = 2$ )
11. Enzyme replacement therapy (idursulfase,  $n = 1$ )
12. NMDA and sigma-1 receptor antagonism (dextromethorphan,  $n = 1$ )
13. Increasing pyruvate dehydrogenase complex (dichloroacetate,  $n = 1$ )
14. Antioxidant (EPI-743,  $n = 1$ )
15. Inhibition of mitochondrial respiratory chain (metformin,  $n = 1$ )
16. Hormonal activity (oxytocin,  $n = 5$ ; thyroxine,  $n = 1$ , liraglutide [glucagon-like peptide 1-receptor agonism],  $n = 1$ ; recombinant human IGF-1,  $n = 1$ ; somatropin,  $n = 1$ )
17. Selective serotonin reuptake inhibition (sertraline,  $n = 1$ )

Of note, we found a RCT on an analogue of the neuropeptide (1–3) IGF-1 (trofinetide), which was approved by the FDA for Rett syndrome during the revision process of the present article (March 2023), so that we did not include this RCT in the count of retrieved RCTs.

Additionally, 3 RCTs tested combination vitamin C and E therapy and one trial investigated coenzyme Q10 therapy.

Fourteen RCTs focused on IDD in fragile X syndrome, 10 on participants with Prader-Willi syndrome, 6 on Rett syndrome, 3 on Down

syndrome, 2 on tuberous sclerosis complex, and 1 each on Dup15q syndrome, pyruvate dehydrogenase complex deficiency, neuropathic or non-neuropathic mucopolysaccharidosis Type II, and Hunter syndrome. Two trials recruited patients with intellectual and developmental disability, testing the effect of investigational products on ADHD symptoms or serious behavioural problems.

Carbetocin was well tolerated and significantly better than placebo in two RCTs (ES not reported) to decrease hyperphagia scores in children/adolescents measured via the Hyperphagia for Prader-Willi Syndrome Questionnaire. In another RCT, oxytocin (Syntocinon) was superior to placebo for hyperphagia scores on the Hyperphagia Questionnaire (HQ)- Total Factor Score but not on the other primary outcomes (HQ- Behavior Factor Score, HQ- Drive Factor Score, and HQ-Severity Factor Score). However, in another RCT, oxytocin was not superior to placebo for hyperphagia in Prader-Willi syndrome. Negative results concerning the primary outcomes were found in RCTs of everolimus (in one RCT, without available results for the other RCT) for individuals with tuberous sclerosis, AFQ056, cannabidiol (1 RCT; results not available for 3 other RCTs), lovastatin, and ganaxolone in fragile X syndrome, dextromethorphan in Rett syndrome, idursulfase in Hunter syndrome, and thyroxine in Down syndrome.

### 3.9. Obsessive compulsive disorder (OCD)

Nine RCTs were found, all but one (88.8%) sponsored by universities/hospitals. Seven modes of action were assessed, including 8 compounds. All identified pharmacological compounds and focused on the following mechanisms of action:

1. Dopaminergic partial agonism (aripiprazole,  $n = 1$ )
2. Selective serotonin reuptake inhibition (fluvoxamine,  $n = 1$ ; note: fluvoxamine has FDA approval in children 8 years old or older; here, participants were 6–17 years)
3. NMDA receptor agonism (D-cycloserine,  $n = 2$ )
4. Enzyme modulation (naproxen sodium,  $n = 1$ ; celecoxib,  $n = 1$ ; note: non-selective and selective cyclooxygenase [COX] inhibition)
5. Immunomodulation (gamunex [immunoglobulin],  $n = 1$ )
6. Glutathione enhancement (N-acetylcysteine,  $n = 1$ )
7. Antibiotic (azithromycin,  $n = 1$ )

The RCT on fluvoxamine was positive (significant difference between fluvoxamine and placebo on the Japanese version of the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS),  $p = 0.044$ , ES not reported). In one RCT (NCT01411774), D-cycloserine was not superior to placebo on the CGI-S (secondary outcome; results not reported for the primary outcome: CY-BOCS). In another RCT recruiting participants with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) and OCD, the difference in the mean decrease in the CY-BOCS score was not significant between the intravenous immunoglobulin Gamunex and the placebo group. Results for the other RCTs were not reported.

### 3.10. Post traumatic stress disorder (PTSD)

We found three RCTs: one, testing sertraline (SSRI) funded by a drug company and two, assessing propranolol (beta-blocker) combined with memory consolidation and reactivation, respectively, sponsored by universities/hospitals. The only RCT with reported results, the one on sertraline, failed to find any significant effect of sertraline vs placebo.

### 3.11. Schizophrenia

Five RCTs were identified, recruiting exclusively individuals aged 17 or younger and testing pharmacological compounds. Of these trials, 60% were funded by drug companies and 40% were sponsored by universities/hospitals. Five modes of action were assessed, including 5

compounds. Mechanisms of action of the compounds assessed in RCTs in schizophrenia included:

1. Dopaminergic, norepinephrine, and serotonergic antagonism (asenapine,  $n = 1$ )
2. Dopaminergic and serotonergic partial agonism (cariprazine,  $n = 1$ )
3. COX-2 inhibition (celecoxib,  $n = 1$ )
4. D-Amino acid oxidase (DAAO) inhibition (sodium benzoate,  $n = 1$ ; note: increasing levels of the NMDA co-agonist D-serine)
5. Glutathione enhancement (N-acetylcysteine,  $n = 1$ )

Asenapine failed to separate from placebo on the Positive and Negative Syndrome Scale (PANSS) Total score (primary outcome), as well as on the subscales of the PANSS and CGI-S (with significant improvement in the CGI-S score observed in the 5 mg b.i.d. group). Results from the other RCTs were not available.

### 3.12. Tourette's syndrome

We retained 12 RCTs, including 1 RCT on a Chinese medicine formula. About 67% (73% when limiting to RCTs of pharmacological agents) were funded by drug companies, the rest were sponsored by universities/hospitals. Six modes of action were assessed, including 7 compounds. Mechanisms of action of the compounds assessed in RCTs in Tourette's syndrome included:

1. Vesicular monoamine transporter-2 inhibition (deutetrabenazine,  $n = 3$ ; valbenazine,  $n = 2$ )
2. Dopaminergic receptor antagonism (ecopipam,  $n = 2$ ; note: selective dopamine D1 receptor antagonist)
3. Norepinephrine receptor agonism (guanfacine XR,  $n = 1$ )
4. Histaminergic (3) receptor antagonism (AZD5213,  $n = 1$ )
5. Cannabinoid receptor agonism (tetrahydrocannabinol + cannabidiol,  $n = 1$ )
6. Glutathione enhancement (N-acetylcysteine,  $n = 1$ )

Positive RCTs with superiority compared to placebo on the primary outcome Yale Global Tic Severity Scale included the one RCT on AZD5213, which was superior to placebo at 2 mg but not 0.5 mg dose (ES, as well as statistical analysis on side effects, not reported), and one of the two RCTs on ecopipam (ES not reported; results not available for the second RCT). Ecopipam was overall well tolerated. Negative RCTs included those on deutetrabenazine (2 out of 3 RCTs, results not reported for the third trial) and both RCTs of valbenazine.

## 4. Discussion

This is, to our knowledge, the first systematic review of phase 2–4 RCTs of compounds across mental health conditions in children and adolescents. About 11% ( $n = 26$ ) of the retrieved RCTs ( $n = 234$ ) had positive findings on  $\geq 1$  primary outcome. The only two compounds with evidence of significant effects that were replicated in  $\geq 1$  additional RCT without any negative RCTs were dasotraline for ADHD – which program was halted by the manufacturer in 2020 – and carbetocin for hyperphagia in Prader-Willi syndrome.

The number of retrieved RCTs was unevenly spread across the childhood mental disorders. The bulk of the retrieved RCTs ( $n = 84$ , 36%) were for ASD, which is likely accounted for by concerns regarding the lack of approved medications for the defining symptoms of this increasingly more recognised and highly impairing condition (Solmi et al., 2022a). A relatively large number of RCTs ( $n = 41$ , 18%) was also found for children with a variety of genetic syndromes associated with IDD and the retrieved RCTs focused on associated mental/physical impairments (e.g., hyperphagia in Prader-Willi syndrome), rather than cognitive or functional abilities per se. Of note, in some RCTs, it was not

clearly reported if IQ was tested. Another relatively large number of RCTs ( $n = 40$ , 17%) was retrieved for ADHD, reflecting the need not only for novel agents, ideally without abuse potential, but also for the approval of licensed agents in pre-schoolers with ADHD, given the increasing attention to this subgroup of children with ADHD (Halperin and Marks, 2019) (Cortese, 2022). By contrast, a limited number of RCTs were found for other conditions in need of additional pharmacological options, such as anxiety disorders, eating disorders, externalizing/disruptive behavior disorders, mood disorders, OCD, and Tourette's syndrome, and data from the majority of the RCTs retrieved for schizophrenia were not available.

The positive findings of the RCTs included in this review should be considered alongside the effect size (ES) and tolerability of the tested compound, and the availability and efficacy of other agents for any specific disorder. Regarding ADHD, given the high effect size of stimulants (in the order of 0.8–1.0) (Cortese, 2020) the moderate effect size reported for dasotraline (0.48), which is comparable to that of atomoxetine (Schwartz and Correll, 2014) and alpha-2 agonists clonidine and guanfacine (Hirota et al., 2014), would position this compound as a possible second- or third-line pharmacological option. Nevertheless, another non-stimulant option could be still valuable for those patients (around 15% in RCTs and probably more in daily clinical practice) where comorbidities such as IDD or ASD may decrease the response rate (Cortese et al., 2021) and/or those who cannot tolerate available medications. Of note, while high dose dasotraline (4 mg/day) was less well tolerated than placebo, at a low dose (2 mg/day), dasotraline did not separate from placebo in terms of tolerability. Further, no serious adverse events were reported in the dasotraline RCTs. However, as mentioned above, the development program for dasotraline was halted by its manufacturer in 2020.

Regarding ASD, while positive individual RCTs focused mainly on associated symptoms and impairment, the search for agents targeting defining symptoms that are supported by replicated evidence continues to be elusive (Barak and Feng, 2016). Since ASD begins very early in life (Solmi et al., 2022b), abnormal biological processes may occur in a time-bound fashion during potentially developmentally vulnerable times that may require specific mechanistic interventions at certain developmental phases (Green et al., 2010).

Regarding depression, positive findings for agomelatine and, partially, for ketamine are promising and welcome, considering the limited range of approved options in children and adolescents (fluoxetine, for youth aged 8–17 years, and escitalopram for those aged 12–17) and the fact that only about 40% of youth have been found to respond to cognitive behavioral therapy (CBT) (March et al., 2004). However, independent replications of the positive findings for agomelatine are required. Regarding ketamine, it should be noted that no significant differences were reported on an additional (i.e., other than the one used as primary outcome) depression scales. Moreover, ketamine was associated with transient, self-limited dissociative symptoms, which calls for further assessment of its safety.

Likewise, the positive findings for AZD5213 and ecopipam in relation to Tourette's syndrome require replication, alongside a better understanding of the specific effect sizes and tolerability. These currently missing data are especially relevant in comparison to alpha-2 agonists, given that the two most common currently used options in clinical care, alpha-2 agonists and D2 antagonists/partial agonists, have been considered to have similar effect sizes for tic severity reduction, but alpha-2 agonists have better tolerability (Whittington et al., 2016), even though a recent network meta-analysis showed superiority of antipsychotic over alpha-2 agonists in terms of efficacy (Farhat et al., 2023). Similarly, for bipolar disorder, more evidence is needed for inositol + omega-3 fatty acids, in particular data on their effect size and tolerability of lithium in preadolescents.

The lack of positive findings for the core symptoms of other disorders reflects several factors including the clinical challenges in conducting RCTs in children and adolescents, possible placebo effects (Huneke

et al., 2022), and the theoretical possibility that some disorders might not be treatable with medications.

Indeed, probably the main conceptual/methodological weakness of the body of research retrieved via our search is the fact that the agent was tested as a “one-size-fits-all” treatment. An exception to this was represented by RCTs in children with IDD, the majority of which included children with IDD within the framework of a genetic syndrome. In these RCTs, the physiological consequences provided the rationale to test specific compounds thought to address the specific pathophysiology of the syndrome. In a few cases only, e.g., in a RCT of the glutamate receptor agonist fasoracetam in children with ADHD with and without mGluR mutations, a stratification of the sample based on neurobiological features was implemented. Therefore, we highlight the potential value of the approach proposed by the Research Domain Criteria framework (Sanislow, 2020), as an opportunity for stratification - including cognitive stratification - of patients to be recruited in RCTs. An additional advantage of this approach rests in the evidence it can provide for transnosographic outcomes (such as irritability/aggressiveness) that are arguably highly relevant in child and adolescent mental health. More research into diagnostic and predictive biomarkers is needed, as these are currently missing in a well-replicated fashion for mental disorders with onset during childhood and adolescence (Cortese et al., 2023).

The limited number of RCTs for schizophrenia, with no positive findings, could seem disappointing. However, first, several dopamine antagonists/partial agonists are already approved and available for adolescents with schizophrenia (Pagsberg et al., 2017). Moreover, we excluded a number of RCTs where adolescents were recruited alongside adults, following more recent guidance by the FDA that considers the option of extrapolation of more limited adolescent data embedded within a larger adult trial program under certain circumstances (FDA, accessed 2023). Of note, we limited our focus to schizophrenia, rather than other psychoses, as their heterogeneous nature would hamper the consistency of findings across RCTs.

Several reasons may explain why relatively few RCTs targeted certain mental health conditions in children and adolescents compared to programmes in adults (Correll, 2023) and only isolated trial programmes and agents yielded positive results. First, at least for conditions that also occur in adults, the drug development pathway tests novel compounds and mechanisms of action in adult populations first. Thus, only agents that were successful/reached regulatory approval in adults are generally tested in children and/or adolescents. Second, mental health conditions in children and adolescents may be developmentally sensitive (Welsh et al., 2020). This creates the possibility that interventions provided outside a specific neurobiological window may not be efficacious (Díaz-Caneja et al., 2021). Third, due to age or neurobiological impairments that encompass language and communication as well as cognitive skills, young individuals with (certain) mental disorders may have difficulties recognizing, describing, and expressing the targeted psychopathology. Here, information from multiple informants may be helpful but also complicates the assessment process (Kraemer et al., 2003). Fourth, while rising placebo effects have plagued all of psychiatry (Correll, 2022), this problem may be enhanced in paediatric mental health RCTs, even more so in children than in adolescents (Parellada et al., 2012; Sifakis et al., 2020) (Faraone et al., 2022).

Our study also informs research governance and reporting practices in the field. We found that 28% of the included RCTs were completed, but their results were not reported. While it is plausible that the effects of the COVID-19 pandemic impacted on the reporting of RCTs, we also found some RCTs for which results were labelled as “not available” in clinicaltrials.gov had indeed been published in articles in peer-reviewed journals. Therefore, we urge authors to promptly update the RCT record in clinicaltrials.gov. Additionally, for some RCTs, mean and standard deviation values for each arm were reported, but not the results of statistical significance tests. Importantly, in the majority of studies, only  $p$  values - which are dependent on sample size - were reported, rather than

standardized effect size, and their 95% confidence intervals. We would urge for more consistent reporting of ES in this field as this would facilitate comparison across RCTs of studied or already available treatment options. This would be more clinically meaningful than solely reporting p-values. Finally, discontinuation of clinical trial programmes and abandonment of compounds should be publicly communicated, alongside the rationale for this.

Our study should be considered in light of some limitations. First, we limited the search from 2010, so we might have missed relevant RCTs registered before this date. However, we deemed a 12-year period as appropriate to retrieve novel agents potentially available for regulatory approval and of interest in day-to-day clinical practice. Second, we may have included agents in this review whose further development has been discontinued by the sponsor without making this decision public. Third, we excluded RCTs recruiting both children/adolescents (until the age of 17) and adults, as separate results for children and adolescents are usually not reported in <https://clinicaltrials.gov/> or <https://www.clinicaltrialsregister.eu/>. Fourth, while we covered a broad range of mental health conditions, our selection did not address all conditions that practitioners could be faced with. More specifically, substance use disorder and enuresis were beyond the scope of this review, the former occurring in an age range overlapping with adulthood and the latter being dealt with more frequently by paediatricians than child and adolescent psychiatrists. Fifth, we included RCTs in which investigated agents were combined with psychotherapeutic or other non-pharmacological interventions, where possible synergistic effects between pharmacological and non-pharmacological interventions cannot be ruled out. However, the combination of pharmacotherapy with psychosocial interventions is guideline-consistent for many, if not most, conditions (e.g. depression (NICE, 2019a), ADHD (NICE, 2019b), and schizophrenia (NICE, 2013)). Sixth, to be comprehensive and provide information about potentially promising agents, we included information on agents sponsored and studied by universities and hospitals, that may not be subjected to the lengthy and costly trial requirements for regulatory approval and, thus, may not achieve marketing authorisation for clinical use. Seventh, we limited the search to two databases (<https://clinicaltrials.gov/> and <https://www.clinicaltrialsregister.eu/>) as we could not include every national database. Eighth, we endeavoured to identify RCTs funded and not funded by drug companies, but where the listed sponsor was a public body this does not automatically equate with a drug company not being involved. Finally, for a sizeable proportion of RCTs, results of statistical analyses on tolerability were not available so we could report only the % of participants in each study arm that experienced serious adverse events or who discontinued the trial due to adverse events.

Despite these limitations, we believe that this review will inform researchers and funders of future priorities and opportunities in the field, and practitioners, patients and their families of possible future treatment options. Alongside drug manufacturers, we hope these findings will be informative also for public funders, fostering their collaborations with academia and research institutes in the field. We also hope there will be additional, well designed RCTs in anxiety, bipolar disorder, disruptive behavior disorders, eating disorders and schizophrenia, for which the number of RCTs is still limited. In this respect, regulatory efforts to promote extrapolation, i.e., the use of relevant information in adults as a basis for the further development of a medicinal product in children or adolescents, are welcome. Indeed, extrapolation has the potential not only to inform better studies in children and adolescents, but also to avoid unnecessary ones. Whilst this review has focused on RCTs, we deem it essential for funders to also support large scale pharmacovigilance studies with the potential to reduce risk of harm. While such studies will likely be expensive, they should be a priority for research funders, given the relevance and impact of their findings.

## Conflict of interest

S Cortese declares honoraria and reimbursement for travel and accommodation expenses for lectures from the following non-profit associations: Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP), and from Healthcare Convention for educational activity on ADHD. M Højlund has been a consultant to or has received honoraria from the Lundbeck Foundation, H. Lundbeck, and Otsuka. C Arango has been a consultant to or has received honoraria or grants from Acadia, Angelini, Biogen, Boehringer, Gedeon Richter, Janssen Cilag, Lundbeck, Medscape, Menarini, Minerva, Otsuka, Pfizer, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. I Baeza has received honoraria and travel support from Angelini, Otsuka-Lundbeck and Janssen. T Banaschewski served in an advisory or consultancy role for eye level, Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche, and Takeda. He received conference support or speaker's fee by Janssen, Medice and Takeda. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press; the present work is unrelated to these relationships. JK Buitelaar has been a consultant to / member of advisory board of / and/or speaker for Takeda, Medice, Angelini, Janssen, Boehringer-Ingelheim and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties. D Coghill served in an advisory or consultancy role for Medice, Novartis, Servier, and Shire/Takeda. He received conference support or speaker's fee from Medice, Servier, and Shire/Takeda. He received royalties from Cambridge University Press and Oxford University Press; He is not an employee of any of these companies, and not a stock shareholder of any of these companies and the present work is unrelated to these relationships. D Cohen has been a consultant or has received honoraria from Janssen/J&J and Otsuka; he served on a Data Safety Monitoring Board for Lundbeck. CU Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Boehringer-Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Newron, Noven, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatrix. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Mindpax, LB Pharma and Quantic. E Grunblatt received grant support from MEDICE Arzneimittel Pütter GmbH & Co KG. C Moreno has received honoraria as a consultant and/or advisor and/or for lectures from Angelini, Esteve, Exeltis, Janssen, Lundbeck, Neuraxpharm, Nuvelution, Otsuka, Pfizer, Servier and Sunovion outside the submitted work. M Parellada has been a consultant to or has received honoraria or grants from Angelini, Janssen Cilag, Exeltis, Lundbeck, Otsuka, Pfizer, Roche, Sage, Servier. A. M. Persico has been a consultant to and/or speaker for and has received honoraria from Servier, Sanofi, and Healx Limited. In the last 3 years, D. Purper-Ouakil reports honoraria/non-financial support from Medice and Shire/Takeda, non-financial support from HAC Pharma, and has worked as an unpaid scientific coordinator for Mensia, all outside the submitted work. In the last 2 years, B Vitiello was a paid consultant for Medice, Menarini, Angelini, and Alkermes Pharmaceuticals. ICKW reports research funding outside the submitted work from Amgen, Bristol Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, Takeda, the Hong Kong Research Grants Council, the Hong Kong Health and Medical Research Fund, the Hong Kong Innovation and Technology Commission, the NIHR, the European Commission, and the Australian National

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#### Data Availability

Data will be made available on request.

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#### Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.neubiorev.2023.105149](https://doi.org/10.1016/j.neubiorev.2023.105149).

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