Effective Health Care Program

Comparative Effectiveness Review
Number 154

Psychosocial and Pharmacologic Interventions for Disruptive Behavior in Children and Adolescents

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This report is based on research conducted by the Vanderbilt Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2012-00009-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States.

These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Psychosocial and Pharmacologic Interventions for Disruptive Behavior in Children and Adolescents

Structured Abstract

Objectives. We systematically reviewed evidence on psychosocial and/or pharmacologic treatment for children with disruptive behavior disorders.

Data sources. We searched MEDLINE® via PubMed® and PsycInfo®, as well as the reference lists of included studies. We used the Comparative Effectiveness Plus interface for the Iowa Drug Information Service (IDIS) database to identify regulatory information.

Review methods. We included studies published in English from January 1994 to June 2014, did dual data extraction, and rated risk of bias and strength of evidence of the literature in accordance with the Agency for Healthcare Research and Quality Methods Guide. We analyzed data qualitatively and quantitatively. Our quantitative analysis was based on a Bayesian estimation approach, and we therefore did not conduct statistical significance tests.

Results. We identified 84 unique studies that addressed one or more Key Questions. Of these, 66 studies assessed psychosocial interventions and 13 assessed pharmacologic interventions. The active treatment arms of studies of psychosocial interventions were categorized as interventions including only a child component (n = 2) or only a parent component (n = 25), or as multicomponent interventions (n = 39). Multicomponent interventions included were defined as including two or more of a child component, parent component, or other component (e.g., teacher, family together). All interventions included in this study that were categorized as multicomponent interventions included a parent component. Studies provided consistent evidence that multicomponent interventions and interventions including only a parent component resulted in significantly greater improvement on parent reports of child disruptive behavior than controls. Our quantitative analysis of the 28 of these studies that met additional criteria for inclusion in our Bayesian multivariate network meta-analysis indicated that all three intervention types were more effective than control conditions. The probability of being the best treatment (i.e., having the largest effect) was the same for multicomponent interventions (43%) and for interventions with only a parent component (43%), followed by interventions with only a child component (14%). Pharmacologic studies evaluated the effectiveness of antipsychotics, antiepileptics, and stimulants and nonstimulants used to treat attention deficit hyperactivity disorder. Studies of antipsychotic medications and valproic acid, an antiepileptic medication, had mixed results over the short term. Two randomized controlled trials (RCTs) of atomoxetine suggested it was more effective at reducing oppositional defiant disorder (ODD) symptoms than placebo. One RCT of guanfacine extended release also reported significant reductions over placebo in ODD symptoms. Two RCTs reported that stimulants were more effective than placebo at reducing ODD and conduct disorder symptoms. We included related publications and an additional four studies to address harms and predictors of treatment effects.

Conclusions. Qualitative and quantitative analyses generally suggest that psychosocial interventions for children with disruptive behavior disorders that include a parent component, either alone or in combination with other components, are likely to be more effective at reducing

disruptive child behaviors than interventions that include only a child component or control conditions. Small studies of antipsychotics and stimulants report positive effects in the very short term. The most commonly reported outcomes are parent-reported outcomes. Long-term and functional outcomes were not consistently reported. There was variability in the duration of long-term followup and functional outcomes reported.

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Executive Summary

Background

Disruptive behavior disorders (DBDs) are a group of related psychiatric disorders of childhood and adolescence marked by temper tantrums, interpersonal aggression, and defiance. These disorders and related symptoms may manifest in young children as significant behavioral problems at home and difficulties at school. Children with disruptive behaviors in early childhood often experience persistent impairment[1] and are at increased risk for negative developmental outcomes, including substance abuse problems; school problems; and delinquent, violent, and antisocial or criminal behaviors in adolescence.[2-14]

DBDs are among the most common child and adolescent psychiatric disorders, with recent estimates indicating that 3.5 percent of children ages 3–17 years had behavioral or conduct problems in the period 2005–11.[15] Examples of DBDs include oppositional defiant disorder (ODD), conduct disorder (CD), attention deficit hyperactivity disorder (ADHD) (as categorized in the fourth edition *Diagnostic and Statistical Manual of Mental Disorders*,[16] reclassified as a neurodevelopmental disorder in the fifth edition[17]), and DBD not otherwise specified.[18-22] Estimates suggest that disruptive behaviors that are problematic but do not meet formal diagnostic criteria may be more common than those meeting formal clinical diagnostic criteria.[2] The etiology of DBDs is unknown, but temperamental, biological, and environmental factors are associated with increased risk.

Although DBD-specific preventive interventions have been developed, practical considerations, including training requirements and cost, pose challenges to broad implementation.[23,24] General outpatient psychotherapy and psychotropic medication management, either alone or in combination with one another, are the interventions most commonly used in the treatment of DBDs.[18,25-28] Psychosocial interventions, including but not limited to psychotherapy, have been developed for some patient subgroups and for some symptoms/symptom clusters. Examples of these interventions include child-level interventions such as cognitive-behavioral therapy (CBT), parent-level interventions such as the Positive Parenting Program (Triple P), and multicomponent interventions such as multisystemic therapy (MST). A wide range of psychotropic medications, including anticonvulsants, antipsychotics, mood stabilizers, and stimulants, have been used to manage children with disruptive behaviors, and their use has increased substantially in recent years. Increasing use has primarily, but not exclusively, been accounted for by increasing use of atypical antipsychotic medications. However, decisional uncertainty exists around the safety and effectiveness of these medications for these childhood disorders.[29]

Scope and Key Questions

DBD symptoms are often present in the absence of a specific DBD diagnosis. Studies that are intended to assess treatments for conditions such as ADHD, for example, are likely to report changes in disruptive behaviors as outcomes. For this reason, and because a review of ADHD currently exists,[30] we focused the current review on studies in which the aim of treatment is specifically a disruptive behavior, with or without a DBD diagnosis, and assessed psychosocial and pharmacologic treatment approaches. We specifically excluded studies of populations of children with ADHD unless the specific focus of treatment was on the non-ADHD disruptive behavior. We also sought studies of concomitant treatment with psychosocial and/or

pharmacologic interventions (i.e., combinations of pharmacologic agents or psychosocial interventions, or medications used in conjunction with psychosocial interventions). We evaluated evidence addressing the following Key Questions (KQs).

Key Questions

KQ1: In children under 18 years of age treated for disruptive behaviors, are any psychosocial interventions more effective for improving short-term and long-term psychosocial outcomes than no treatment or other psychosocial interventions?

KQ2: In children under 18 years of age treated for disruptive behaviors, are alpha-agonists, anticonvulsants, beta-blockers, central nervous system stimulants, first-generation antipsychotics, second-generation (atypical) antipsychotics, and selective serotonin reuptake inhibitors more effective for improving short-term and long-term psychosocial outcomes than placebo or other pharmacologic interventions?

KQ3: In children under 18 years of age treated for disruptive behaviors, what is the relative effectiveness of any psychosocial interventions compared with the pharmacologic interventions listed in KQ2 for improving short-term and long-term psychosocial outcomes?

KQ4: In children under 18 years of age treated for disruptive behaviors, are any combined psychosocial and pharmacologic interventions listed in KQ2 more effective for improving short-term and long-term psychosocial outcomes than individual interventions?

KQ5: What are the harms associated with treating children under 18 years of age for disruptive behaviors with either psychosocial or pharmacologic interventions?

KQ6a: Do interventions intended to address disruptive behaviors and identified in KQs 1–4 vary in effectiveness based on patient characteristics, including sex, age, racial/ethnic minority, family history of disruptive behavior disorders, family history of mental health disorders, history of trauma, and socioeconomic status?

KQ6b: Do interventions intended to address disruptive behaviors and identified in KQs 1–4 vary in effectiveness based on characteristics of the disorder, including specific disruptive behavior or disruptive behavior disorder (e.g., oppositional defiant disorder, conduct disorder, aggression), concomitant psychopathology (e.g., attention deficit hyperactivity disorder or substance abuse), related personality traits and symptom clusters, presence of comorbidities (other than concomitant psychopathology), age of onset, and duration?

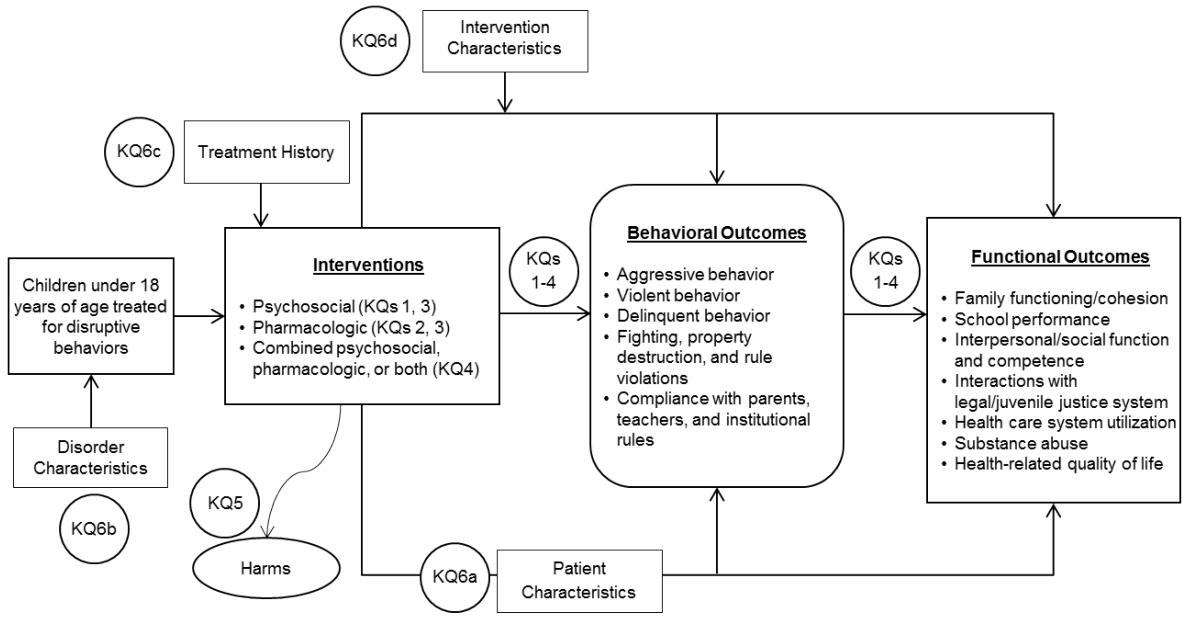
KQ6c: Do interventions intended to address disruptive behaviors and identified in KQs 1–4 vary in effectiveness based on treatment history of the patient?

KQ6d: Do interventions intended to address disruptive behaviors and identified in KQs 1–4 vary in effectiveness based on characteristics of the treatment, including duration, delivery, timing, and dose?

Analytic Framework

The analytic framework (Figure A) illustrates how a psychosocial (KQs 1, 3), pharmacologic (KQs 2, 3), or combined (KQ4) intervention for children under 18 years of age treated for disruptive behaviors may result in changes to one or more behavioral outcomes (KQs 1–4), functional outcomes (KQs 1–4), or harms (KQ5). Behavior outcomes include aggressive behavior; violent behavior; delinquent behavior; fighting, property destruction, and rule violations; and compliance with parents, teachers, and institutional rules. Functional outcomes include family functioning/cohesion; school performance; interpersonal/social function and competence; interactions with legal/juvenile justice system; health care system utilization; substance abuse; and health-related quality of life. Patient characteristics (KQ6a), disorder characteristics (KQ6b), treatment history (KQ6c), and treatment characteristics (KQ6d) may change intervention treatment effects.

Figure A. Analytic framework



Methods

Literature Search Strategy

To ensure comprehensive retrieval of relevant studies, we used the following key databases: the MEDLINE® medical literature database (via the PubMed® interface), EMBASE, the Cochrane Central Register of Controlled Trials, and PsycInfo®. We used the Comparative Effectiveness Plus interface for the Iowa Drug Information Service (IDIS) database to identify regulatory information from the following sources: Food and Drug Administration (FDA) approval packages, FDA Advisory Committee Reports, boxed warnings, clinical practice guidelines, Agency for Healthcare Research and Quality (AHRQ) Evidence Reports and Comparative Effectiveness Reviews, and National Institute for Health and Clinical Excellence (NICE) Clinical Guidelines or Technology Appraisal Guidance. We also searched other sources (e.g., Clinicaltrials.gov, meeting abstracts, FDA) for context and relevant data, as well as ongoing trials.

Search strategies (presented in Appendix A of the full report) included broad terms for psychosocial interventions and pharmacologic agents, as well as including interventions by name (e.g., "Parent-Child Interaction Therapy," "Incredible Years®," and "Triple P - Positive Parenting Program®" [Triple P]). We used hand searching of recent systematic reviews and other relevant publications to identify additional studies not captured by the database searches. The randomized controlled trials (RCTs) included to assess efficacy were used to assess harms. AHRQ contracts with the Scientific Resource Center (SRC) to obtain information from drug manufacturers. We requested scientific information packets and regulatory information from SRC for individual pharmacologic agents. We received responses from 3 of the 20 requests and confirmed that the studies referenced in the information packets were included in our literature searches.

Inclusion and Exclusion Criteria

Eligible studies had to be published in English in or after 1994, focus on the treatment of disruptive behavior, and include children exhibiting disruptive behaviors as a primary problem (e.g., CD, ODD, and intermittent explosive disorder). We excluded studies published before 1994 because our preliminary search found that in articles published 20 or more years ago, the study populations were inadequately described, rendering a large number of the older studies unusable for this review. We excluded studies of preventive interventions for an at-risk population because our review was focused on studies of individuals who met a clinical threshold for a DBD. We required that eligible studies include a comparison group (i.e., controlled trials, cohort studies). We excluded studies of disruptive behavior secondary to other conditions (e.g., treatment of substance abuse, developmental delay, intellectual disability, and pediatric bipolar disorder). In the case of ADHD, we excluded studies of ADHD-related disruptive behaviors but included studies of non–ADHD-related disruptive behaviors in populations of children with ADHD if the children were identified as also having another DBD. Our quantitative analysis further excluded studies that did not report baseline and end-of-treatment means and standard deviations using one of the three most commonly used outcome measures. Explicit inclusion and exclusion criteria are documented in the abstract screening form and full-text screening form (Appendix B of the full report) and described in more detail in the full report.

Study Selection

Two reviewers independently assessed each abstract. If one reviewer concluded that the article could be eligible based on the abstract, we retained it for review of the full text. Two reviewers independently assessed the full text of each included study, with any disagreements adjudicated by a senior reviewer.

Data Extraction and Synthesis

We extracted data from included studies into evidence tables that report study design, descriptions of the study populations (for applicability), description of the interventions, and baseline and outcome data on constructs of interest. Data were initially extracted by one team member and reviewed for accuracy by a second.

Data are presented in summary tables and analyzed qualitatively in the text. We also employed Bayesian multivariate mixed-treatment (network) meta-analytic methods using data on a subset of included studies (n = 28) that met additional criteria for inclusion in the meta-analysis. These additional criteria were that a study was an RCT that employed one or more of the three most prevalent measures of child disruptive behavior in this literature, and reported means and standard deviations at baseline and end of treatment on these measures. To account for the large number of specific interventions employed by the constituent studies, we classified each arm of each included study as an intervention with only a child component, an intervention with only a parent component, or a multicomponent intervention. Multicomponent interventions were defined as those that included two or more of a child component, parent component, or other component (e.g., teacher component, family together component). We considered study treatment arms not identified as one of these three classes as wait-list control or treatment as usual.

Recognizing that these treatment categories are broad and encompass a range of specific interventions, each specific intervention was modeled as a random effect, allowing for variation in treatment effect within each class because of factors not explicitly modeled.

Our primary outcomes for analysis and strength of evidence were parent reports of child disruptive behaviors as assessed using the most common validated measures, such as subscales of the Eyberg Child Behavior Inventory (ECBI) and the Child Behavior Checklist (CBCL).

Risk-of-Bias Assessment of Individual Studies

We used the Cochrane Risk of Bias Tool[31] to assess risk of bias for RCTs of effectiveness. Reviewers rated six items from five domains of potential sources of bias (i.e., selection, reporting, performance, detection, and attrition) and one item for other sources of bias. To assess risk of bias for study designs other than RCTs, we used the RTI Item Bank[32] for nonrandomized controlled studies, and the AMSTAR (A Measurement Tool to Assess Systematic Reviews) tool[33] for systematic reviews and meta-analyses. To assess the risk of bias associated with the reporting of harms, we used an adapted version of the McMaster Assessment of Harms Tool.[34] Appendix C of the full report includes questions used in each tool. Two team members independently assessed each included study, with discrepancies resolved through discussion to reach consensus and/or adjudication by a senior reviewer. The results of these assessments were then translated to low, moderate, or high risk-of-bias designations, as described in the full report. Risk-of-bias ratings are in Appendix C of the full report.

Strength of the Body of Evidence

Two senior investigators graded the body of evidence for key intervention/outcome pairs using methods based on the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[35] The team reviewed the final strength-of-evidence (SOE) designation. The possible grades were:

- High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates.
- Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change confidence in the estimate of effect and may change the estimate.
- Low: Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is likely to change the estimate.
- Insufficient: Evidence is either unavailable or does not permit a conclusion.

Applicability

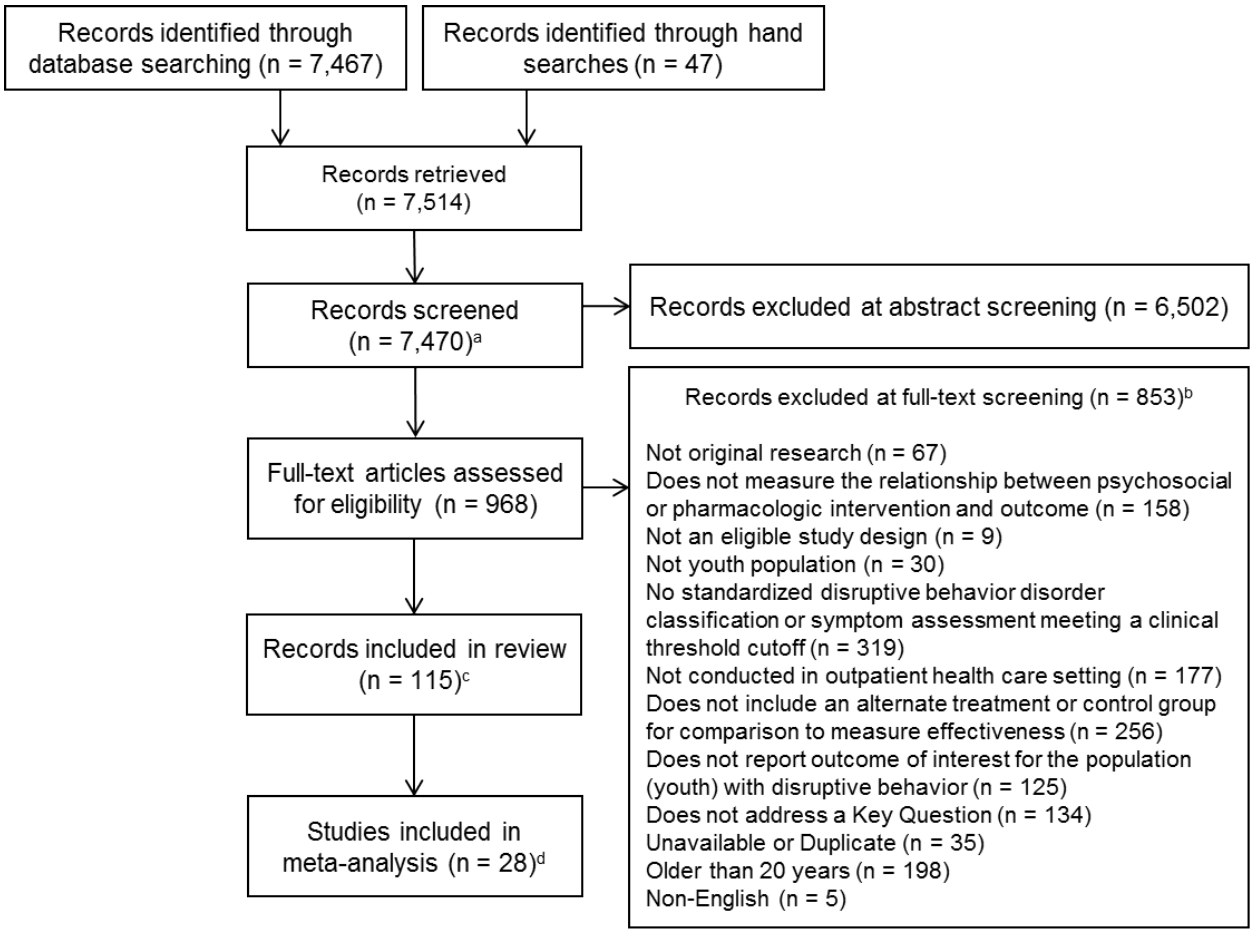
We assessed applicability by identifying potential population, intervention, comparator, outcome, timing, and setting (PICOTS) factors likely to affect the generalizability of results (i.e., applicability to the general population of children and adolescents being treated for disruptive behaviors). We considered factors related to difficulties identifying the target population, the availability of interventions, characteristics of the population such as socioeconomic status and family environment that may be associated with disruptive behaviors, and setting of the intervention as particularly likely to affect applicability.

Results

Article Selection

We identified 7,470 nonduplicative titles or abstracts with potential relevance, with 968 proceeding to full-text review. We excluded 853 studies at full-text review and included 84 unique studies (115 publications) in the review (Figure B). We present findings by intervention and outcome area where possible under each KQ. Sixty-six studies addressed psychosocial interventions (KQ1); 13 addressed pharmacologic interventions (KQ2). In addition to studies of effectiveness, we identified five additional studies that exclusively addressed KQ5 (n = 4) and KQ6 (n = 1). Studies of psychosocial interventions were heterogeneous. We categorized interventions as child focused, parent focused, or multicomponent (i.e., 2 or more of a child, parent, or other type of intervention component). Pharmacologic interventions were antipsychotics, antiepileptics, and two groups of drugs typically used to treat ADHD (stimulants and nonstimulants).

Figure B. Literature flow diagram



[a]Excluding discarded duplicates (n = 44).
[b]Records could be excluded for more than one reason.
[c]115 publications representing 84 unique studies.
[d]A subset of studies (n = 28) met eligibility criteria for inclusion in a quantitative analysis.

KQ1. Effectiveness of Psychosocial Interventions Compared With Other Psychosocial Interventions or No Treatment

Sixty-six studies (59 RCTs and 7 non-RCTs) addressed the effectiveness of psychosocial interventions.

Preschool Children

Twenty-three studies (10 high, 11 moderate, and 2 low risk of bias) evaluated psychosocial interventions for preschool children (under age 5). The active treatment arm in 14 studies consisted of interventions that included only a parent component, and 9 studies were multicomponent. No studies in this age group were of interventions that included only a child component. Most (17 of 23) studies assessed one of three interventions: Incredible Years® (IY) (n = 5), Parent-Child Interaction Therapy (PCIT) (n = 7), or Triple P (n = 5). The six other studies each evaluated a distinct intervention.

Three of the five IY studies evaluated only the parent-training component and reported significant improvements on multiple validated measures in the active treatment versus control arms. Among studies reporting outcomes using the ECBI Intensity scale, effect sizes ranged from 0.70 to 0.89. Outcomes did not differ between groups in the other two studies.

All studies assessing Triple P (n = 5) and PCIT (n = 7) reported significantly improved disruptive behaviors as measured by the ECBI Intensity and/or Problem scales in the active treatment versus control arms. Individual Triple P studies reported different measures of clinical significance, with estimates including 23 to 70 percent of children in the treatment arms experiencing clinically significant reliable change on parent reports of child disruptive behavior, 33 to 40 percent of children in the treatment arms remaining above the clinical cutoff on the ECBI Intensity scale, or 25 to 30 percent still meeting diagnostic criteria for DBD.

Individual PCIT studies also reported different measures of clinical significance, with PCIT effects reported as 67 to 100 percent of children in treatment arms experiencing clinically significant change, 56 to 68 percent still meeting ODD diagnostic criteria, or effect sizes for PCIT ranging from 0.83 to more than 3.0.

School-Age Children

Twenty-nine studies (9 high, 19 moderate, and 2 low risk of bias) evaluated psychosocial interventions for school-age children (ages 5–12 years) with disruptive behaviors. The active treatment arm of 1 study was an intervention with only a child component, 11 studies were of interventions with only a parent component, and 18 were studies of multicomponent interventions. Approximately half of the studies (15/29) assessed one of five programs: IY (n = 7), the Parent Management Training Oregon (PMTO™) model (n = 2), Coping Power Program (n = 2), Stop Now and Plan™ Under 12 (SNAP Under 12) Outreach Project (n = 2), and a modular intervention (n = 2). The other studies each assessed a different intervention.

Three of the studies examining the IY intervention examined only the parent-training component in comparison with control. Two of these reported that the treatment arm experienced significantly reduced ECBI Intensity and Problem scales versus control arms (range of reduction on ECBI Intensity scale, 14% to 20% for treatment vs. 4% to 5% for control; range of reduction on ECBI Problem scale, 40% to 47% for treatment vs. 14% to 20% for control). One study reported no difference between groups on the CBCL Externalizing subscale.

The other four IY program studies examined multiple combinations of the child, parent, and teacher training programs with one another and with control arms. Given multiple group

comparisons and multiple outcome measures, results are inconsistent and difficult to summarize succinctly. Two studies reported that the arm with only parent training resulted in greater improvement in child disruptive behavior than control: one study used the ECBI Intensity scale and CBCL Aggression subscale; the other study used the ECBI Intensity scale and CBCL Total Problems scale. Two studies reported that combined parent and child training resulted in significantly reduced disruptive behaviors compared with control, but results were inconsistent across measures, with one study showing significant reductions on the CBCL Aggression subscale but not on the ECBI Intensity scale, and the other study showing significant reductions on both the CBCL Total Problems scale and the ECBI Intensity scale. Finally, one study using teacher-reported aggression as the outcome reported that the combined parent and child training resulted in greater improvement than either the parent training only or control, but that there was no difference between the parent training only and control arms.

The two studies comparing PMTO with treatment as usual both reported significant reductions from baseline to end of treatment, one study reporting 10 percent versus 7 percent change in mean CBCL Externalizing subscale scores and the other reporting 15 percent versus 8 percent mean change in ECBI Intensity scale scores for treatment and control arms, respectively. One of the two studies examining the Coping Power Program reported a 35-percent reduction in Parent Daily Report (PDR) scores at end of treatment over baseline, relative to 17-percent reduction in the comparison arm, but did not report significant differences between groups on other measures of child disruptive behavior; the other study of this intervention did not report significant between-group differences. The two studies evaluating the SNAP ORP both reported significant differences between treatment and control arms on the CBCL Aggression subscale, with percent change from baseline to end of treatment ranging from 10 to 16 percent in the treatment arms relative to 2 to 6 percent in the control arms. Significant changes were also seen on other CBCL subscales. The two studies examining the modular intervention essentially tested its portability and did not include a control arm.

Teenage Children

Fourteen studies (5 high, 5 moderate, and 4 low risk of bias) assessed psychosocial interventions for adolescents (ages 13–17 years) with disruptive behaviors. The active treatment arm of 1 study included only a child component, and 13 studies were of multicomponent interventions. The 13 multicomponent intervention studies included 5 studies of Multisystemic Therapy (MST), 3 studies of Brief Strategic Family Therapy® (BSFT), and 1 study of each of 6 different multicomponent interventions.

Four of the five MST studies reported that MST was associated with greater reductions in disruptive behaviors in comparison with control arms, but studies used different outcome measures, making it difficult to report summary effects succinctly. One study defined criminal offenses as its primary outcome measure and reported that the proportion with offenses decreased more significantly over time for teenagers in the MST versus control arm ($p < 0.001$) but did not report significant between-group differences over time on the CBCL Externalizing subscale. One study reported small effect-size differences between MST and treatment as usual on a number of measures, with a 0.12 difference favoring MST in effect sizes for CBCL Externalizing subscale scores (MST effect size, 0.56; tau effect size, 0.44). One study reported significant improvements in MST completers versus individual therapy completers on multiple outcome measures, including child disruptive behaviors as assessed with the Symptom Checklist-90-Revised (SCL-90-R) ($p < 0.05$), family relations as assessed with the 30-item

Family Adaptability and Cohesion Evaluation Scale (FACES-II) ($p < 0.05$), and observational measures of parent-child relations ($p < 0.001$). Finally, one study examined differences between MST and treatment as usual on a number of measures, with effect sizes for parent-reported child disruptive behaviors on the CBCL Externalizing subscale of $d = 0.47$ and $d = 0.28$, respectively ($p < 0.05$).

The three studies of BSFT each reported significant improvements in disruptive behaviors. One study reported reliable improvement of 43 percent in BSFT versus 11 percent in control groups on a CD symptom measure and improvement of 36 percent in BSFT versus 11 percent in control arms on a measure of social aggression. The other two BSFT studies, one examining girls referred for bullying behavior and the other examining boys referred for bullying behavior, both reported significant mean differences in an index score of adolescent risk-taking behavior of −9.3 for BSFT relative to controls ($p < 0.001$) for girls and −6.3 for BSFT relative to controls ($p < 0.001$) for boys.

Meta-Analysis

Results from our Bayesian multivariate mixed treatment (network) meta-analysis on the subset of studies from the qualitative review that met the additional criteria (described previously) for being included in our meta-analysis ($n = 28$) were generally consistent with results from our qualitative synthesis. We defined intervention categories that classified each study arm of each included study as including only a child component, including only a parent component, a multicomponent intervention, or control. Multicomponent interventions were defined as those that included two or more of a child component, parent component, or other component (e.g., teacher component, family together component). All interventions categorized as multicomponent interventions included a parent component. Control arms were defined to include treatment as usual or wait-list control arms. Recognizing that these treatment categories are broad and encompass a range of more specific interventions, we modeled each specific intervention as a random effect. Results from our quantitative analysis indicated that the probability of being best was 43 percent for both multicomponent interventions and for interventions with only a parent component. The probability of being best was 14 percent for interventions with only a child component. The marginal posterior probabilities of remaining above the clinical cutpoint (i.e., exhibiting significant disruptive behavior) at end of treatment on the specific measures included in our meta-analysis (ECBI, CBCL) were nominally higher for the comparison group relative to each intervention group, with multicomponent interventions showing the lowest proportion of children still above the clinical cutpoint post-treatment. Although we considered age-by-treatment interactions, there was not enough balance among the age and treatment combinations to include them in the final model.

KQ2. Effectiveness of Pharmacologic Agents Compared With Other Agents or Placebo

Thirteen studies (12 RCTs and 1 non-RCT) of pharmacologic interventions met criteria for inclusion. No studies were of drugs with an FDA indication for DBD. We considered one RCT to have low risk of bias, seven RCTs to have moderate risk of bias, and four RCTs to have high risk of bias. We considered one nonrandomized study to have high risk of bias. These studies fall into four major categories: antipsychotic or antiepileptic drugs (typically targeted to aggression), and a group of drugs comprising both stimulants and nonstimulants (typically used in children

with comorbid ADHD). Only one study was federally funded; the rest were industry sponsored or partially funded by a pharmaceutical company.

Studies of antipsychotics had mixed results over the short term. Three RCTs (all high risk of bias) addressed risperidone (as initial treatment, to augment stimulants, or as maintenance treatment) compared with placebo. Two studies were small, with 20 and 25 participants, and one was large (n = 355). All were short term (1 to 6 months). In one study, aggression scores and Clinical Global Impressions-severity (CGI-S) ratings decreased significantly in the risperidone arm compared with placebo (mean aggression change of −1.9 vs. −0.7; p = 0.0007 and mean CGI-S change of −2.46 vs. −1.06; p = 0.01). Another RCT of risperidone as a stimulant adjunct also assessed aggression and reported no significant group differences at followup, and the third RCT, of maintenance with risperidone, reported increases in conduct problems and severity in both groups (increases in Nisonger conduct problem ratings of 5.0 [9.5] in the treatment group and 8.8 [11.2] in placebo), with no significant group differences.

One RCT with high risk of bias (n = 46) assessed aripiprazole compared with ziprasidone and reported no significant group differences in aggression, and another RCT comparing quetiapine and placebo (n = 19) reported no significant parent-rated changes in aggression but clinician-rated changes on the CGI-S (mean followup score of 3.4 for the treatment group vs. 5.0 for placebo; effect size, 1.6; 95% confidence interval, 0.9 to 3.0; p = 0.007).

Results were also mixed in three small RCTs (n = 121) of valproic acid, an antiepileptic, with two placebo-controlled studies favoring the intervention (53% to 86% in the treatment arms vs. 8% to 25% in placebo arms considered much improved on the Clinical Global Impressions-improvement (CGI-I) scale or Overt Aggression Scale; p <0.01) and another with no significant difference demonstrated.

Two RCTs (1 moderate and 1 high risk of bias) examined the nonstimulant ADHD medication atomoxetine. Both studies reported that atomoxetine was more effective than placebo in reducing ODD symptoms in children with comorbid ADHD and ODD (oppositional behavior score mean change, −2.7 vs. −0.3 in 1 study; in a second study, 48.3% to 55.7% of atomoxetine participants improved by at least 30% compared with 35.6% of the placebo group). Parent-rated quality of life improved significantly in the atomoxetine group (mean change, 2.6 points) compared with placebo (mean change, −1.6 points) in one RCT.

One RCT of guanfacine extended release with moderate risk of bias reported significant reductions in ODD symptoms compared with placebo (least-square mean change from baseline, −10.9 for guanfacine extended release vs. −6.8 for placebo; p <0.001; effect size, 0.59), again among children with comorbid ADHD and ODD. One RCT with high risk of bias reported that treatment with an extended-release formulation of mixed amphetamine salts significantly improved ODD symptoms compared with placebo (mean change of −0.23 to −0.43 among amphetamine dosage groups vs. −0.30 in placebo group; p = 0.024). Another RCT reported that methylphenidate treatment reduced CD symptoms compared with placebo as rated by parents and teachers. Duration of all studies was short, with a range of 4 to 9 weeks, and no studies reported functional outcomes beyond statistically significant shifts on scales, commonly the Overt Aggression Scale and CGI.

KQ3. Effectiveness of Psychosocial Interventions Compared With Pharmacologic Interventions

No head-to-head studies were identified that directly compared psychosocial with pharmacologic interventions for DBD.

KQ4. Effectiveness of Combined Psychosocial and Pharmacologic Interventions Compared With Individual Interventions

No head-to-head studies were identified that assessed the comparative effectiveness of combination interventions.

KQ5. Harms of Psychosocial or Pharmacologic Interventions

Harms of psychosocial interventions are not reported in the literature. The pharmacologic treatment studies in this report were generally small and short term, with typically no followup post-treatment. Studies were powered for effectiveness and not for detection of harms, so harms may be underrepresented in the published literature. Generally, harms reported in included studies were mild or moderate and immediate in nature. Nonetheless, there was significant loss to followup in several pharmacologic studies, some of which was likely due to adverse events. We therefore sought harms data from other sources that might include more extensive and longer term data, including other systematic reviews and FDA package labeling. It is important to note that harms of atypical antipsychotics have been studied extensively, including in recent AHRQ reviews, and the high relative risk of metabolic outcomes is a known adverse effect, particularly for atypical antipsychotics.

In effectiveness studies included in this report, frequently occurring adverse events associated with risperidone included weight gain, sedation, and somnolence. In the largest risperidone study (n = 527), the percent of participants experiencing weight gain ranged from 1.2 to 6.5 across risperidone phases and was 0.6 percent in the placebo arm. Somnolence occurred in 1.7 to 11.6 percent of children receiving risperidone and in 1.2 percent of children receiving placebo. At least 35 percent of children in the acute, continuation, and maintenance risperidone dosing phases and those receiving placebo experienced an adverse event, and extrapyramidal symptoms occurred in less than 2 percent of participants in each phase. Sedation was the most frequently reported harm in a study comparing aripiprazole (sedation occurring in 50% of children) and ziprasidone (sedation occurring in 57% of children), while harms were generally reported more often in the placebo group in an RCT comparing quetiapine and placebo. Decreased mental alertness, diminished emotional expression, and diminished facial expression occurred significantly more frequently in the placebo group than with quetiapine (p values $\leq$0.03).

Adverse events associated with mixed amphetamine salts included sleep delay, insomnia, and anorexia, with mean weight loss ranging from 1.1 to 3.3 pounds across dosage groups. One study of methylphenidate also reported delayed sleep but did not present harms data. Atomoxetine was most frequently associated with fatigue (21.3% to 35% of children in slow- and fast-titration groups and 10.2% of placebo group), nausea (19.7% to 21.7% of treatment groups and 5.1% of placebo), and headache (14.8% to 25% of treatment groups and 15.3% of placebo) in one RCT and with anorexia (33.6% of treatment group) and somnolence (29.9% of treatment group) in another. Guanfacine was associated with somnolence (50.7% of treatment group and 5.1% of placebo) and headache (22.1% of treatment group and 17.9% of placebo).

Also provided in the main report is a summary of FDA labeling data, as well as prior reviews of harms associated with the included drugs. Rates of harms from those sources were typically higher than rates of harms reported in the short-term effectiveness studies and may provide a more complete picture of potential harms. They do not, however, place the harms data in the context of tradeoffs with effectiveness.

KQ6. Factors That Modify Effectiveness of Interventions

We identified 24 studies (37 publications) that addressed KQ6. This question was divided into subquestions about variations in intervention effectiveness due to (a) patient characteristics, (b) characteristics of the disorder, (c) patient treatment history, and (d) treatment characteristics. It is unclear if studies identified as examining these questions were adequately powered to answer them.

We identified 12 studies examining variations in psychosocial intervention effectiveness due to patient characteristics. In general, results were inconsistent, although some evidence exists that the child's sex, maternal characteristics such as depression and anger, and other family functioning variables are associated with the effectiveness of some psychosocial interventions.

Results were inconsistent regarding the effects of baseline severity. One study of preschool children reported that greater severity of behavior problems was associated with greater improvements, but no effect of baseline severity was reported in another study. In a study of school-age children, concomitant developmental delay was associated with less effectiveness of the intervention. In two studies including adolescents, lower levels of psychopathology were associated with better disruptive behavior outcomes. No studies examined whether the effectiveness of psychosocial interventions varied by patient treatment history. Dose of intervention was examined as a treatment characteristic that might mediate intervention effectiveness, but results appear to be inconsistent, with two studies reporting more improvements when parents attended a higher number of training sessions or completed more homework than when they did not and one study reporting no differences in outcomes among children who attended more CBT sessions than those who attended fewer sessions. For psychosocial interventions that include a parent component, either alone or in combination with other components, there is some evidence suggesting that improved parenting practices partially mediate effectiveness. Improvements in child outcomes were associated with positive parenting changes in three studies of preschool children and in three of four studies of school-aged children.

Few studies of pharmacologic interventions reported moderator or mediator analyses. One RCT assessing mixed amphetamine salts reported that changes in aggression ratings were higher for those children with greater baseline ODD severity. One study indicated that atomoxetine was more effective in patients who had previously been treated with a stimulant than in patients who had not.

Discussion

Key Findings

Sixty-six studies examined the effectiveness of psychosocial interventions for children with disruptive behaviors. About half of the studies (n = 25) were conducted in the United States; the remaining studies were conducted in Australia (n = 11), Canada (n = 4), Germany (n = 3), Ireland (n = 2), Israel (n = 2), Italy (n = 1), Netherlands (n = 5), Norway (n = 4), Puerto Rico (n = 1), Sweden (n = 3), and the United Kingdom (n = 5). Twenty-three studies examined psychosocial interventions with preschool-age children, 29 studies examined psychosocial interventions with school-age children, and 14 studies examined psychosocial interventions with adolescents. Interventions in each study's active treatment arm were categorized as including only a child component (n = 2), only a parent component (n = 25), or multiple components (n =

39). Multicomponent interventions were defined as those that included two or more of a child component, parent component, or other component (e.g., teacher component, family together component). All interventions categorized as multicomponent included a parent component. Most of the studies examining psychosocial interventions that met criteria for this review used parent reports of child disruptive behaviors as the primary outcome, most commonly the ECBI or CBCL. Seventeen of the 23 studies examining psychosocial interventions for preschool-age children assessed one of three programs (IY, PCIT, and Triple P). In general, studies provided consistent evidence that each of these interventions resulted in significantly greater improvement on parent reports of child disruptive behavior than controls. Most of the studies examining psychosocial interventions for school-age children examined one of the following programs: IY, PMTO, Coping Power Program, SNAP Under 12, or a modular intervention. In general, included studies provided consistent evidence that IY, PMTO, and SNAP Under 12 resulted in significantly greater improvement on parent reports of child disruptive behaviors than controls. Eight of the 14 studies examining psychosocial interventions for adolescents assessed either MST or BSFT. In general, these studies provided consistent evidence that each of these interventions resulted in significantly greater improvement on parent reports of child disruptive behavior than controls.

Results from our Bayesian multivariate mixed-treatment (network) meta-analysis were generally consistent with our qualitative synthesis. Results indicated that the probability of having the largest effect was the same for multicomponent interventions (43%) and interventions with only a parent component (43%). The probability of having the largest effect was 14 percent for interventions with only a child component. The marginal posterior probabilities of remaining above the clinical cutpoint (i.e., exhibiting significant disruptive behavior) at end of treatment on the specific measures included in our meta-analysis (ECBI, CBCL) were nominally higher for the comparison group relative to each intervention group, with multicomponent interventions showing the lowest proportion of children still above the clinical cutpoint post-treatment. Although we considered age-by-treatment interactions, there was not enough balance among the age and treatment combinations to include them in the final model.

Despite a fairly robust literature on psychopharmacologic drugs as a whole, we identified only 13 studies evaluating short-term outcomes of pharmacologic interventions for inclusion in our review. Medical studies fall into four major categories; antipsychotic or antiepileptic drugs (typically targeted to aggression in children)[36] and a group of drugs comprising both stimulants and nonstimulants typically used in children with comorbid ADHD. Of the 12 RCTs, one was assessed as low risk of bias and only one was federally funded. The duration of studies was short, with a range of 4 to 9 weeks. Studies of antipsychotic medications and valproic acid, an antiepileptic medication, had mixed results over the short term. Two RCTs of atomoxetine suggested that it was more effective at reducing ODD symptoms than placebo. One RCT of guanfacine extended release also reported significant reductions over placebo in ODD symptoms. Two RCTs reported that stimulants were more effective than placebo at reducing ODD and CD symptoms.

No head-to-head studies were identified that compared the effectiveness of combined psychosocial and medical interventions or that compared the effectiveness of psychosocial interventions with medical interventions.

No harms of psychosocial interventions were sought or reported. The pharmacologic treatment studies in this report were generally small and short term, with typically no followup post-treatment. Thus, harms reported in those studies were generally mild or moderate and fairly

immediate in nature. Nonetheless, there was significant loss to followup in several studies, some of which was likely due to experiencing adverse events, and we therefore sought harms data from other sources that might include more extensive and longer term data, including other systematic reviews. It is important to note that harms of atypical antipsychotics have been studied extensively, including in recent AHRQ reviews. Adverse events associated with risperidone were generally mild across studies, with weight gain, sedation, and somnolence frequently reported. Sedation was frequently reported with aripiprazole and ziprasidone. Adverse events associated with mixed amphetamine salts included sleep delay, insomnia, and anorexia. Atomoxetine was associated with anorexia and headache. Guanfacine was associated with somnolence and headache.

Although we identified studies that examined whether variations in intervention effectiveness due to (a) patient characteristics, (b) characteristics of the disorder, (c) patient treatment history, and (d) treatment characteristics could be found, it is not clear that the studies were adequately powered to answer these questions. Studies are relatively homogeneous with respect to child age, perhaps implicitly recognizing the potential for child age to modify the effectiveness of both psychosocial and pharmacologic interventions. Twelve studies were identified that examined variations in psychosocial intervention effectiveness due to patient characteristics. In general, results were inconsistent, although some evidence exists that the sex of the child, maternal characteristics such as depression and anger, and other family functioning variables are associated with the effectiveness of some psychosocial interventions.

The most commonly examined characteristic of DBD that might affect intervention effectiveness is baseline severity of child disruptive behaviors and/or the presence of comorbid psychiatric conditions. Results were inconsistent. Some studies suggested that difficult temperament in preschool children and psychopathy in teenagers modified the effectiveness of psychosocial interventions.

No studies examined whether the effectiveness of psychosocial interventions varied by patient treatment history, and one study reported that atomoxetine was more effective in patients who had previously been treated with a stimulant than it was in patients who had not.

Potential mediators of treatment effect were most thoroughly examined in the literature on psychosocial interventions. The variables most commonly examined include baseline severity of symptoms, intervention dose, and positive parenting. In general, there is some support that each of these variables may mediate intervention effectiveness, but results were inconsistent.

Existing Systematic Reviews

We located reviews published from 2005 to 2014 and evaluated each for relevance to our KQs using the review PICOTS (Appendix B of the full report). We identified 22 reviews assessing the effectiveness of psychosocial interventions and 2 reviews assessing the effectiveness of pharmacologic interventions. These reviews are described in the Discussion chapter of the full report.

Strength of Evidence

The evidence to answer KQs about interventions for children with disruptive behavior disorders was insufficient to moderate. Tables A and B (and Tables 49-51 in the full report) summarize the strength of the evidence and provide the assessment of the risk of bias, consistency of findings across trials, directness of the evidence, and precision of the estimate provided by the literature. To assess publication bias in the pharmacologic literature, we sought

study protocols and data from regulatory sources and compared this information with the results in the published literature. We assessed strength of evidence for the effectiveness of interventions using the qualitative and quantitative approaches described in the Methods section.

Table A. Summary of evidence in studies addressing the effectiveness of psychosocial interventions targeting parenting practices on parent-reported changes in disruptive behaviors (KQ1)

Age Category	Intervention Category	Key Outcome(s)	SOE Grade	Findings
Preschool (n = 23)	Child-only interventions (n = 0)	NA	Insufficient	No studies were identified.
	Parent-only interventions (n = 14)	Parent-rated disruptive behaviors	Moderate SOE for positive effects of intervention on child behavior	13 RCTs (5 high, 7 moderate, 1 low risk of bias) and 1 non-RCT with moderate risk of bias were identified. Parent reports of child disruptive behavior outcomes were consistently improved in parenting intervention arms compared with wait-list or treatment-as-usual controls. Differences between modified versions of the same intervention were typically not significant.
	Multicomponent interventions (n = 9)	Parent-rated disruptive behaviors	Moderate SOE for positive effects of intervention on child behavior	9 RCTs (5 high, 3 moderate, 1 low risk of bias) were identified. Parent reports of child disruptive behavior outcomes consistently improved in multicomponent intervention arms compared with wait-list or treatment-as-usual controls. Differences between modified versions of the same intervention were typically not significant.
School age (n = 29)	Child-only interventions (n = 1)	Parent-rated disruptive behaviors	Insufficient	1 RCT with moderate risk of bias reported improvement on parent reports of child disruptive behavior from baseline in both intervention and control groups but no between-group differences.
	Parent-only interventions (n = 11)	Parent-rated disruptive behaviors	Moderate SOE for positive effects of intervention on child behavior change	8 RCTs (2 high, 5 moderate, and 1 low risk of bias) and 3 non-RCTs with high risk of bias were identified. Parent reports of child disruptive behavior consistently improved in intervention groups vs. control, but differences between modified versions of the same intervention were not significant.
	Multicomponent interventions (n = 17)	Parent-rated disruptive behaviors	Low SOE for positive effects of intervention on child behavior change	15 RCTs (3 high, 11 moderate, 1 low risk of bias) and 2 non-RCTs (1 high, 1 moderate risk of bias) were identified. Parent reports of child disruptive behaviors improved from baseline in most active treatment arms but between-group changes were not consistently significantly different. The same effects as measured by multiple scales within an individual study were not always consistent.

Table A. Summary of evidence in studies addressing the effectiveness of psychosocial interventions targeting parenting practices on parent-reported changes in disruptive behaviors (KQ1) (continued)

Age Category	Intervention Category	Key Outcome(s)	SOE Grade	Findings
Teenage (n = 14)	Child-only interventions (n = 1)	Parent-rated disruptive behaviors	Insufficient	1 study with high study limitations was identified.
	Parent-only interventions (n = 0)	NA	Insufficient	No studies were identified.
	Multicomponent interventions (n = 13)	Parent-rated disruptive behaviors	Moderate SOE for positive effects of intervention on child behavior change	12 RCTs (3 high, 5 moderate, 4 low risk of bias) and 1 RCT with high risk of bias were identified. Parent reports of child disruptive behaviors indicated improved outcomes in treatment arms vs. control arms in most studies. Differences between modified versions of the same intervention were typically not significant.

KQ = Key Question; NA = not applicable; RCT = randomized controlled trial; SOE = strength of evidence

Table B. Summary of evidence in studies addressing the effectiveness of pharmacologic interventions (KQ2)

Intervention	Key Outcome(s)	SOE Grade	Findings
Antipsychotics	Disruptive behaviors	Moderate SOE for the effectiveness of antipsychotics in achieving statistically significant improvements in measures of disruptive behaviors over the short term	3 of 3 RCTs reported significantly greater improvements in treatment group compared with control. Studies were funded by industry and should be replicated by groups without appearance of conflict.
	Aggression	Insufficient	There were inconsistent and imprecise outcomes and small numbers of participants (n = 64) in 3 short-term RCTs and 1 cohort study with medium study limitations. Aggression improved significantly in the treatment group vs. control in 1 RCT, there were no group differences in 1 RCT and 1 cohort study, and there was worsening of outcomes in both groups in 1 RCT with no group differences. SOE grade is insufficient due to conflicting results.
Stimulants (methylphenidate, amphetamine)	Disruptive behaviors	Low SOE for positive effects on disruptive behaviors	In 2 studies with high risk of bias that used different outcome measures, the treatment groups improved significantly more than placebo (p values ≤0.05).
Nonstimulants (atomoxetine, guanfacine)	Disruptive behaviors	Moderate SOE for positive effect on disruptive behaviors	3 RCTs had medium study limitations, adequate sample size (n = 537), and statistically significant change scores of 0.59 to 0.69.

Table B. Summary of evidence in studies addressing the effectiveness of pharmacologic interventions (KQ2) (continued)

Intervention	Key Outcome(s)	SOE Grade	Findings
Divalproex	Aggression	Low SOE for improvement or remission of aggressive behavior	Improvement in aggression was more than 3 times as likely in treated vs. untreated participants in 3 small RCTs with medium study limitations.
High-dose vs. low-dose divalproex	Aggression	Insufficient	In 1 study with medium study limitations, more participants in the high-dose arm than low-dose arm were considered much improved (53% vs. 8%; p <0.0008).

KQ = Key Question; NA = not applicable; RCT = randomized controlled trial; SOE = strength of evidence

Applicability

The populations studied in both the psychosocial and pharmacologic literature were predominantly male. Approximately half of the studies of psychosocial interventions were of school-age children. We defined a study as focusing on school-age children if it had a sample with a mean age of 5 to 12 years. We established 5 years of age as the lower bound because this is the age at which children typically begin attending kindergarten in the United States. We established 12 years of age as the upper bound because 13 years is regarded as the beginning of adolescence in casual parlance. For precisely these reasons, the age group classification both has face validity in the United States and is somewhat arbitrary.

In addition to the age group definition, our definition of the target population included only children with disruptive behaviors who received treatment in health care settings. We did not restrict our study population to children meeting formal diagnostic criteria for DBD. Rather, we included children without a diagnosed DBD but with disruptive behaviors above a measure-specific threshold on well-validated measures of child disruptive behavior. This may limit applicability to real-world clinical settings.

Applicability of our findings is also limited by restricted access in real-world clinical settings to some of the interventions most commonly examined in the studies included in this review. A vast majority of studies were in the outpatient setting, and they were generally carried out at academic medical centers in the United States. Children served in these settings may differ in important ways from children in other clinical settings.

Many of the pharmacologic studies were very small, and results may not be broadly generalizable. None of the interventions has a specific indication for disruptive behaviors, although they are widely used for these conditions in the United States. Interventions included antipsychotic drugs, an antiepileptic drug, and ADHD drugs (both stimulants and nonstimulants). Of particular importance, all but three of the studies on pharmacologic interventions either were sponsored directly by pharmaceutical companies or were conducted by individuals who are highly supported by those companies. Similarly, many of the psychosocial interventions were evaluated by the developer.

The studies also did not address the effectiveness of psychosocial interventions delivered concurrently with pharmacologic interventions or the common concern of polypharmacy, and thus there may be limited ability to assess applicability in highly complex cases. In reality, many if not most children and adolescents receiving treatment for disruptive behaviors may have multiple codiagnoses and other complex challenges.

Research Gaps

Research needs are both substantive and methodological, and they include both conduct and reporting of research. Randomization and allocation procedures were not adequately described, and blinding was not attempted or addressed in much of the psychosocial literature (KQ1). Future research should also clearly describe the duration of time from baseline to post-treatment and post-treatment to followup, and more clearly describe results from mixed models. Because the psychosocial intervention developer is often the researcher, existing research must be replicated, as the lack of replication introduces the potential for a risk of bias analogous to that introduced by industry-sponsored trials of pharmaceutical interventions.

With no categories of drugs meeting the criteria for high SOE, more research needs to be conducted across the range of potential pharmacologic interventions (KQ2). Importantly, this research should be funded by independent parties, rather than primarily the pharmaceutical industry. Substantially more information is warranted on modifiers of effectiveness by subgroup and on harms of intervention. Longer term studies are essential, as children may remain on medications over substantial periods.

There is a need for specific head-to-head comparisons of psychosocial interventions, evaluation of the effectiveness of psychosocial interventions compared with pharmacologic interventions (KQ3), and evaluation of the effectiveness of combined psychosocial and pharmacologic interventions (KQ4). Parents need this information to make informed decisions about which treatments to seek for their children. Clinicians need answers to these questions to decide which interventions to be trained to deliver and to recommend to their patients. Policymakers need this information to determine how to incentivize providers to provide the care for which there is the most evidence of effectiveness.

Future research should also clearly identify the target population and address the portability of studied interventions from predominantly university research clinics to real-world clinical settings. In the United States, disruptive behaviors are more prevalent among children receiving publicly funded care, who are therefore likely to receive treatment in clinical settings such as community mental health centers. This group of young people may differ in important ways from the children receiving treatment in university-based research clinics. These concerns are consistent with the growing body of literature about the challenges of implementing and disseminating best practices to real-world clinical settings with fidelity.

Limitations of the Evidence Base

There are a number of limitations of the evidence base for this review—some specific to the literature on psychosocial interventions, some specific to the literature on pharmacologic interventions, and some crosscutting.

One important limitation of the psychosocial intervention literature (KQ1) is that, although most included studies were RCTs, overall the literature suffered from a lack of clear identification of primary outcomes and of random-sequence generation and allocation-concealment procedures. In addition, there was frequently no attempt to achieve blinding. Although there are well-recognized and valid reasons that achieving this level of control in studies of these types of interventions is challenging, it brings potential risk of bias into the literature. The lack of clearly identified primary outcomes likely reflects a lack of consensus on the most important outcomes; there are few studies that measure similar outcomes for synthesis. Methodologically, outcomes such as direct observation by a blinded and independent observer

are arguably the most valid. However, direct observations can be expensive and are not always logistically feasible. From the perspective of patient-centered outcomes research, we believe that there is a strong argument to be made in favor of the importance of parent-reported outcomes, even though in the absence of blinding they introduce a risk of bias, because most psychosocial interventions included a parent component. Further, results from mixed models are not always presented in a straightforward manner, making it very difficult to tease out effects of specific treatment approaches.

The issue of publication bias in psychological science is difficult to address, given the current lack of standards regarding the registration of study protocols in social sciences. We attempted to minimize the potential for bias introduced by the "file drawer effect" (i.e., nonpublication of studies with nonsignificant results) by expanding the literature search to include unpublished sources (e.g., meeting abstracts) and asking Key Informants about current research or developments in the field that may not yet be published.

Few studies focused on treating disruptive behaviors with pharmacologic interventions. The drugs used for this purpose are frequently used off label and without a research basis for their use in this particular set of disorders. Many of the studies include mixed populations and report outcomes of overlapping symptoms (e.g., of ADHD and DBD), making it difficult to discern the degree to which the mitigation of ADHD, for example, is in fact driving the results. Most of the studies in this section were small; larger studies are clearly needed. Because of the small number of studies on medication use for DBDs in children, we did not use a formal statistical approach to assess the possibility of publication bias, as it would be unlikely to be informative. We did, however, seek study protocols and records from the FDA and Clinicaltrials.gov to assess reporting as a component of the SOE assessment. We did not find evidence that reporting bias was likely.

Limitations applying equally to the literature on both psychosocial and pharmacologic interventions are difficulties inherent in identifying the target population and the potential for bias introduced by conflicts of interest. We included in our review both studies of children with a formal diagnosis of DBD and children without a formal diagnosis of DBD who scored above a clinical cutoff on a well-validated measure of child disruptive behaviors. A lack of detail in reporting by authors makes it challenging to characterize the populations in the studies.

Conflict of interest is a concern in this evidence base. Most of the studies evaluating a psychosocial intervention for a child disruptive behavior included in this review were conducted either by the developer of the intervention or by an "intellectual descendant" of the developer. Although it is understandable for this to be the case (as it is common to see industry-sponsored clinical drug trials), the strength of the evidence for this body of literature would be strengthened with more studies independently evaluating the interventions.

Finally, there are few direct comparisons of individual interventions and no studies evaluating the efficacy of both behavioral and pharmacologic interventions compared with pharmacologic or behavioral interventions alone (KQ3 or KQ4). Specific interventions were most often compared with a wait-list control group or treatment as usual (variably described).

Conclusions

This review generally suggests that psychosocial interventions for children with DBD that are either multicomponent interventions or interventions that include only a parent component appear likely to be more effective at reducing disruptive child behaviors than interventions that include only a child component or control conditions. Given that all of the multicomponent

interventions included in this study contained a parent component in combination with at least one other component (child component, family component, teacher component, other component), it seems reasonable to conclude that a parent component is important. Very few studies directly support the effectiveness of pharmacologic interventions for children with DBD, but small studies of antipsychotics and stimulants report positive effects in the very short term. No studies examined the effectiveness of these interventions in combination with one another. The most commonly reported outcomes are parent-reported outcomes. Long-term and functional outcomes were less consistently reported. There was variability in the duration of long-term followup and functional outcomes reported.

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Background

Disruptive Behavior Disorders (DBDs) are a group of related psychiatric disorders of childhood and adolescence marked by temper tantrums, interpersonal aggression, and defiance. These disorders and related symptoms may manifest in young children as significant behavioral problems at home and difficulties at school. Children with the highest levels of disruptive behavior in early childhood, often experience persistent impairment[1] and are at increased risk for negative developmental outcomes including substance abuse problems, school problems, and delinquent, violent, and antisocial or criminal behaviors in adolescence.[2-14]

DBDs are among the most common child and adolescent psychiatric disorders, with recent estimates indicating that 3.5% of children between the ages of 3-17 years had behavioral or conduct problems from 2005-2011.[15] Examples of DBDs include Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), attention deficit hyperactivity disorder (ADHD) (as categorized in the fourth edition Diagnostic and Statistical Manual of Mental Disorders;[16] re-classified as a neurodevelopmental disorder in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders)[17] and disruptive behavior disorder not otherwise specified.[18-22] Estimates suggest that disruptive behaviors that are problematic but do not meet formal diagnostic criteria may be more common than those meeting formal clinical diagnostic criteria.[2] The etiology of DBDs is unknown, but temperamental, biological, and environmental factors are associated with increased risk.

DBDs are associated with increased risk for a wide range of negative developmental outcomes including substance abuse problems, school problems, and delinquent, violent, and antisocial or criminal behaviors.[2-14] As many of these problems persist into adulthood, the economic costs of DBDs are high. The etiology of DBDs is unknown but temperamental, biological and environmental factors are associated with increased risk. Temperamental risk factors include callous-unemotional traits, behavioral disinhibition, and indicators of limited executive functioning such as having a short attention span.[23] Biological risk factors include lower salivary cortisol levels, lower baseline heart rate levels, and higher increases in heart rate in response to frustration.[24,25] Low birthweight children also are at increased risk for DBDs.[26,27]

Environmental risk factors include prenatal exposure to maternal smoking, substance use, illness, and stress.[26] Children who have experienced abuse and neglect, early separation from their parents including adoption, and maternal anxiety and depression are also at increased risk.[26] Risk attributable to factors such as maternal smoking, substance use, and anxiety and depression during pregnancy have been addressed by more general public health campaigns. Although DBD-specific preventive interventions have been developed, practical considerations including training requirements and cost pose challenges to broad implementation.[28,29]

Treatment

General outpatient psychotherapy and psychotropic medication management are the most commonly used interventions, either alone or in combination.[18,30-33] Psychosocial interventions have been developed for some patient subgroups and for some symptoms/symptom clusters. Examples of these interventions include child-level interventions such as Cognitive-Behavioral Therapy (CBT); parent-level interventions such as the Positive Parenting Program (Triple P); and multicomponent interventions such as Multisystemic Therapy (MST).[34-41]

The use of psychotropic medications to manage disruptive behaviors has increased dramatically and has primarily, but not exclusively, been accounted for by increasing use of

atypical antipsychotic medications.[31-33,42] Using data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, Cooper and colleagues[31] demonstrated that antipsychotic prescribing increased nearly five-fold from 8.6 per 1,000 U.S. children in 1995-96 to 39.4 per 1,000 U.S. children in 2001-02. Furthermore, the medication prescribing increases were greater for non-approved indications including DBDs than for approved indications such as schizophrenia, psychosis, Tourette's syndrome, autism, and mental retardation.

There is wide range of medications used with a significant degree of decisional uncertainty around safety, efficacy, and which combinations to use.[43] Classes of medications that have been studied for treatment of disruptive behaviors include antipsychotics, mood stabilizers, anticonvulsants, and psychostimulants.[44] Combination therapy with antipsychotics and stimulants is commonly used for patients with attention deficit hyperactivity disorder (ADHD) comorbid with DBD or aggression;[45] however, superiority over monotherapy and tolerability of combined pharmacologic treatment is unclear.

Systematic Reviews and Guidelines

We identified a number of systematic reviews and meta-analyses published recently evaluating pharmacotherapy for youth with disruptive behaviors.[45-53] Other recent reviews evaluated the effectiveness of parenting programs, cognitive behavior therapies, social skills, and other nonpharmacologic treatments such as acupuncture and dietary supplementation.[54-63]

The recently published Treatment of Maladaptive Aggression in Youth guidelines[64,65] from the Center for Education and Research on Mental Health Therapeutics (CERT) recommend psychosocial interventions and address the use of combination therapy. The guidelines suggest initial medication management and psychosocial treatments to address any underlying condition, followed by use of an antipsychotic or mood stabilizer to treat persistent aggression.[64,65] Data from high quality studies are needed to confirm these recommendations.

Antipsychotic drugs have FDA approval for a limited set of specific indications in children, including bipolar and irritability associated with autism, although not for Disruptive Behavior Disorder. Nonetheless, pediatric use of both first and second-generation antipsychotics has rapidly increased in recent years, including in conditions for which they are not FDA indicated. Recent reviews have concluded that there is an absence of evidence from controlled studies on the long-term efficacy and safety of these drugs in children.[66] Although there is a recent review of antipsychotics for pediatric patients, this review is not specific to disruptive behavior disorders and concludes that there are important gaps in the literature on the comparative effectiveness and relative safety of these drugs.[67] The authors of a systematic review of antipsychotic and psychostimulant drug combination therapy for ADHD and DBD noted that most studies were performed over short time periods, and several studies lacked blinding.[45]

A review from the Substance Abuse and Mental Health Services Administration (SAMHSA) describes "promising" practices for treatment and prevention of disruptive behaviors in children.[68] Despite the existence of these and other reviews of pharmacologic and psychosocial interventions, there remains an absence of clear and accessible guidance for best practice.

Wide variations in clinical management of DBDs, including the use of polypharmacy and tailored psychosocial approaches, frequently administered with little to no adherence to a standard protocol, are described in the literature. In the absence of clearly synthesized information about which interventions are most safe and effective for specific patient subgroups, it is difficult for healthcare providers to make informed treatment recommendations. For

example, individual studies of Problem-Solving Skills Training and Parent-Child Interaction Therapy have reported positive results for children with DBDs, but it is unclear how healthcare providers should select between a child-level intervention, a parent-level intervention, a multicomponent intervention, and pharmacotherapy. The role of early risk factors, family ecology, and treatment history on treatment response remains unclear. Treatment decision dilemmas are further complicated for patients with medical and/or psychiatric comorbidities. The safety of atypical antipsychotics also is an important concern.[45,50-52]

Scope of the Review

DBDs are a heterogeneous group of conditions; disruptive behaviors are also heterogeneous and are often present in the absence of a specific DBD diagnosis. Studies that are intended to assess treatment for conditions such as ADHD, for example, are likely to report changes in disruptive behaviors as outcomes. For this reason, and because a review of ADHD currently exists,[69] we focused the current review on studies in which the aim of treatment was specifically a disruptive behavior, with or without a DBD diagnosis. We excluded studies focusing on treating ADHD and other conditions that may include disruptive behaviors, (e.g., autism, developmental disability) but are not intended to assess treatments focused on reducing disruptive behaviors themselves.

This review specifically focused on psychosocial and pharmacologic interventions for disruptive behavior. We also sought studies of combined or co-interventions (i.e., combinations or pharmacologic agents or psychosocial intervention, or medication used in conjunction with psychosocial interventions). We included studies of parent-targeted psychosocial interventions if the study reported changes to child disruptive behavior. For pharmacologic interventions, we targeted the literature on their use in disruptive behavior disorders, focusing on a smaller but more focused literature base. The choice of outcomes on which to focus the analysis and particularly the strength of evidence was challenging for this review. Many different measures are used to assess components of disruptive behavior, not all of which have been validated. We extracted data on behavioral and functional outcomes and emphasized the use of validated measures, particularly the ECBI and CBCL for conducting strength of evidence assessments and in the meta-analysis.

We outline the population, interventions, comparators, outcomes, timing, and setting for the review in the PICOTS (Table 1).

Table 1. PICOTS

PICOTS	Criteria and Key Question(s)
Population	• Children under 18 years of age who are being treated for disruptive behavior or a disruptive behavior disorder (KQs 1-6)
Intervention(s)	• Psychosocial intervention (KQs 1, 3-6) • Pharmacologic intervention (KQs 2-6) • Combined psychosocial and pharmacologic intervention (KQs 4-6)
Comparator	• Alternate psychosocial or pharmacologic intervention • Inactive treatment, including waitlist control, active treatment, and placebo

Table 1. PICOTS (continued)

PICOTS	Criteria and Key Question(s)	
Outcomes	Behavioral outcomes (KQs 1-4, 6) • Aggressive behavior • Violent behavior • Delinquent behavior • Fighting, property destruction, and rule violations • Compliance with parents, teachers, and institutional rules Functional outcomes (KQs 1-4, 6) • Family functioning/ cohesion • School performance • Interpersonal/social function and competence • Interactions with legal/juvenile justice system • Health care system utilization • Substance abuse • Health related quality of life	Adverse effects / Harms (KQ 5) • Metabolic effects: weight gain, hyperglycemia and diabetes, hyperlipidemia • Extrapyramidal effects: parkinsonism, acute dystonia, akathisia, tardive dyskinesia • Cardiac adverse effects: prolonged QT/arrhythmias, hypotension, cardiomyopathy • Prolactin-related effects • Allergic reaction • Sudden death • Suicide • Over-medication or inappropriate medication • Negative effects on family dynamics • Stigma • Other harms, as reported
Timing	• Any length of followup (KQs 1-6)	
Setting	• Clinical setting, including medical or psychosocial care that is delivered to individuals by clinical professionals, as well as individually focused programs to which clinicians refer their patients. Excludes school wide or system wide settings wherein interventions are targeted more widely. (KQs 1-6)	

KQ = Key Question; PICOTS = population, comparator, outcomes, timing, setting

Key Questions

The treatments for disruptive behaviors and disruptive behavior disorders include both psychological and pharmacologic approaches. Nonpharmacologic interventions usually are recommended as the initial strategy, but clinicians and families are likely to use both approaches at some point, possibly simultaneously, creating further decisional dilemmas related to co-therapy, polypharmacy, and the role of treatment history. We therefore framed the Key Questions to ascertain the comparative effectiveness of various psychological and pharmacologic treatments aimed at disruptive behaviors, compared both within and between treatment types, and ascertain whether there are combinations of psychological and pharmacologic therapeutic approaches that are optimal.

Key Question 1: In children under 18 years of age treated for disruptive behaviors, are any psychosocial interventions more effective for improving short-term and long-term psychosocial outcomes than no treatment or other psychosocial interventions?

Key Question 2: In children under 18 years of age treated for disruptive behaviors, are alpha-agonists, anticonvulsants, beta-blockers, central nervous system stimulants, first-generation antipsychotics, second-generation (atypical) antipsychotics, and selective serotonin reuptake inhibitors more effective for improving short-term and long-term psychosocial outcomes than placebo or other pharmacologic interventions?

Key Question 3: In children under 18 years of age treated for disruptive behaviors, what is the relative effectiveness of any psychosocial interventions compared with the pharmacologic interventions listed in Key Question 2 for improving short-term and long-term psychosocial outcomes?

Key Question 4: In children under 18 years of age treated for disruptive behaviors, are any combined psychosocial and pharmacologic interventions listed in Key Question 2 more effective for improving short-term and long-term psychosocial outcomes than individual interventions?

Key Question 5: What are the harms associated with treating children under 18 years of age for disruptive behaviors with either psychosocial or pharmacologic interventions?

Key Question 6a: Do interventions intended to address disruptive behaviors and identified in Key Questions 1-4 vary in effectiveness based on patient characteristics, including sex, age, racial/ethnic minority, family history of disruptive behavior disorders, family history of mental health disorders, history of trauma, and socioeconomic status?

Key Question 6b: Do interventions intended to address disruptive behaviors and identified in Key Questions 1-4 vary in effectiveness based on characteristics of the disorder, including specific disruptive behavior or disruptive behavior disorder (e.g., oppositional defiant disorder, conduct disorder, aggression), concomitant psychopathology (e.g., attention deficit hyperactivity disorder or substance abuse), related personality traits and symptom clusters, presence of comorbidities (other than concomitant psychopathology), age of onset, and duration?

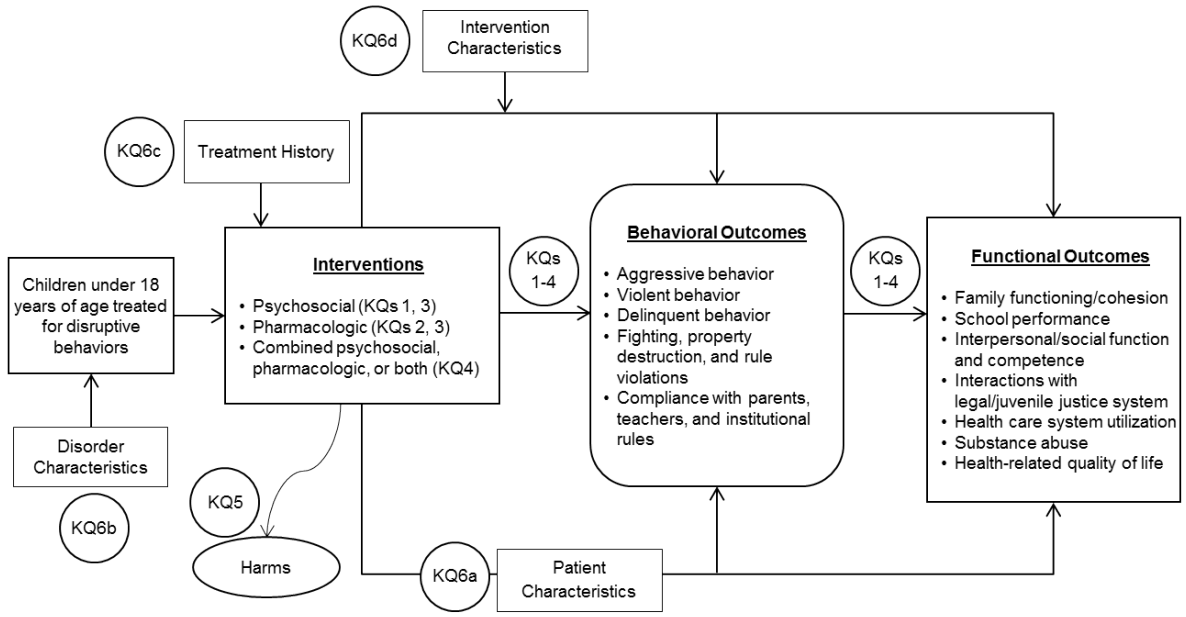
Key Question 6c: Do interventions intended to address disruptive behaviors and identified in Key Questions 1-4 vary in effectiveness based on treatment history of the patient?

Key Question 6d: Do interventions intended to address disruptive behaviors and identified in Key Questions 1-4 vary in effectiveness based on characteristics of the treatment, including duration, delivery, timing, and dose?

Analytic Framework

The analytic framework (Figure 1) illustrates the population, interventions, outcomes, and adverse effects that will guide the literature search and synthesis.

Figure 1. Analytic framework



Organization of This Report

We have organized the report by Key Question. For Key Question 1 (psychosocial interventions) we present the studies by age (categorized as preschool, school-age, and adolescent) and then further divide the sections by single or multiple intervention components. For Key Question 2 (pharmacologic interventions) we present the study information by study drug categories. For Key Question 5 we present the harms information from included studies, existing reviews, and gray literature. We limited the meta-analysis to Key Question 1 and more specifically to those outcomes reported using a common and validated outcome measure for disruptive behavior.

Methods

Topic Refinement and Review Protocol

Initially a panel of key informants gave input on the Key Questions (KQs) to be examined; these KQs were posted on the Agency for Healthcare Research and Quality (AHRQ) website for public comment for 4 weeks and revised as needed. We drafted a protocol for the review and recruited technical experts to provide content and methodological expertise on the development of the review.

Searching for the Evidence

Search Strategy

Searches were executed between September 2013 and June 2014. We conducted search update during peer review of the draft report. We developed search strategies using a combination of subject headings (i.e., controlled vocabulary) and keywords (Appendix A).We included broad terms for psychosocial interventions, as well as interventions by name (e.g., "Parent-Child Interaction Therapy", "Incredible Years", and "Positive Parenting Program"). We included terms to describe drug classes and individual agents. We built the search strategies in tandem with the refinement of the KQs and Analytic Framework to ensure that the literature retrieval was representative of the project scope. The preliminary results were vetted by clinical and methodologic subject matter experts. We did not conduct a separate search for longitudinal cohort studies of adverse events, but did conduct a separate search for existing systematic reviews and requested drug package inserts to obtain information on harms.

Databases

To ensure comprehensive retrieval of relevant studies, we used the following key databases: the MEDLINE medical literature database (via the PubMed interface), EMBASE, and PsycInfo®. We used the Comparative Effectiveness Plus interface for The Iowa Drug Information Service (IDIS) database to identify regulatory information from the following sources: Food and Drug Administration (FDA) approval packages, FDA Advisory Committee Reports, boxed warnings, Priority Clinical Practice Guidelines, AHRQ Evidence Reports and AHRQ Comparative Effectiveness Reviews, Pivotal Studies, National Institute for Health and Clinical Excellence (NICE) Clinical Guidelines or Technology Appraisal Guidance.

Hand Searching

We used hand searching of recent systematic reviews and other relevant publications to identify additional studies not captured by the database searches. We also reviewed the references lists of the included studies.

Gray Literature

We searched the websites of agencies/organizations as well as other sources (e.g., Clinicaltrials.gov, meeting abstracts, FDA) for context and relevant data, in the area of treatment for disruptive behavior disorders in children. We retrieved the medical and statistical evaluations for relevant drugs from the FDA (www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049872.htm).

For KQ5, we reviewed and extracted information from package inserts, regulatory sources, and unpublished data for all relevant drug interventions to identify data on harms and side effects.

Scientific Information Packets (SIPs)

We requested Scientific Information Packets (SIP) and regulatory information from the Scientific Resource Center (SRC) for individual pharmacologic agents. The SRC SIP coordinator requested information from industry stakeholders and managed the information retrieval. We received responses from three of the 20 requests and confirmed that the studies referenced in the information packets were included in our literature searches.

Screening

We conducted two levels of screening using explicit inclusion and exclusion criteria and documented the assessments using an abstract screening form and full text screening form (Appendix B). The abstract screening form contained questions about the primary exclusion and inclusion criteria for initial screening. We used a more detailed form (full-text screening form) to examine the full-text of references that met criteria for inclusion in abstract review.

Initially, we reviewed the titles and abstracts from all references retrieved by the literature and hand searches. References that met the prespecified criteria for inclusion, as determined by one reviewer, were promoted for second level screening (i.e., full text review). To be excluded at the abstract screening level, two reviewers had to determine, independently, that a reference did not meet one or more criterion for inclusion. Conflicts (i.e., disagreements between reviewers) were promoted for a second level review, as were references with insufficient information to make a decision about eligibility.

All references promoted to full text review were screened by at least two reviewers against the inclusion/exclusion criteria. Discrepancies were resolved by a senior team member or through team consensus. We retained the citations for all retrievals, and recorded the screening results and complete inclusion and exclusion data.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the review were derived from our understanding of the literature, refinement of the review topic with the Task Order Officer and Key Informants, and feedback on the KQs obtained during the public posting period.

Population

The target population for this review is children under 18 years of age who are being treated for a disruptive behavior (Table 2). Eligible studies had to focus on the treatment of the disruptive behavior and include children exhibiting disruptive behaviors as a primary problem (e.g., conduct disorder, oppositional defiant disorder, and intermittent explosive disorder). We considered also, studies that included subjects who were not diagnosed with a disorder but who were being treated for disruptive behaviors that were measured by and found to be above the clinical cutoff on a validated measure.

Table 2. Case definition for disruptive behavior

Case Definition for Disruptive Behavior
Behaviors that "violate the rights of others (e.g., aggression, destruction of property) and/or that bring the individual into significant conflict with societal norms or authority figures."[a] The review will include studies that look at children exhibiting these behaviors as a primary problem, such as the DSM-5 disruptive behaviors disorders like Conduct Disorder, Oppositional Defiant Disorder, and Intermittent Explosive Disorder, though some studies will include subjects who have not been diagnosed with one of these disorders but who are being treated for disruptive behaviors such as early onset aggression. This review will exclude studies where disruptive behaviors are studied as symptoms or comorbidities (e.g., substance abuse, Autism Spectrum Disorder, Pervasive Developmental Disorder, developmental delay, intellectual disability, and Attention Deficit Hyperactivity Disorder, etc.).

[a]American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth edition. Arlington, VA: American Psychiatric Association; 2013. Available at: dsm.psychiatryonline.org.

We included studies of interventions that targeted parents of children with a disruptive behavior if the study explicitly defined the eligible patient population to include a child with a disruptive behavior (as defined above) and the study reported one or more child outcome. We excluded studies of disruptive behavior secondary to other conditions (e.g., treatment of substance abuse, developmental delay, intellectual disability, pediatric bipolar disorder). In the case of ADHD, we excluded studies of ADHD-related disruptive behaviors but included studies of non-ADHD-related disruptive behaviors in populations of children with ADHD if the children were identified as also having another disruptive behavior disorder. Our quantitative analysis further excluded studies that did not report baseline and end of treatment means and standard deviations using one of the three most commonly used outcome measures.

Interventions

We sought studies of psychosocial interventions such as: behavior management training, social skills training; cognitive-behavioral therapy; functional behavioral interventions; parent training; dialectical behavior training; psychotherapy; and contingency management methods. Studies of parent- or family-focused interventions were included if the study included children with a DBD (as defined above) and measured and reported at least one child behavior or functional outcome. We included studies that evaluated an intervention targeting the health or wellbeing of the parent or caretaker of a child with DBD only if the study reported child outcomes. For the purposes of this review, we did not include information technology-based and assisted services, media, diet, or exercise.

We did not include studies of prevention in asymptomatic, undiagnosed, or at-risk participants because we wanted to focus our review on children with disruptive behaviors that would be treated if they presented in healthcare settings. We focused our review on studies that included children who scored above the clinical threshold on a validated scale and/or who were formally diagnosed with a DBD. We did not include studies designed exclusively to assess, measure, screen, or diagnose disease or symptoms. We did not include universal interventions such as those implemented in the school setting, studies of systems-level interventions, or studies of interventions targeting organizational delivery of care. Other excluded interventions were: dietary supplements and specialized diets; allied health interventions (e.g., speech/language therapy, occupational, and physical therapy); complementary and alternative medicine interventions (e.g., acupuncture, herbal, and folk remedies); physical activity and recreational programs (e.g., yoga, exercise training); and invasive medical interventions (e.g., surgery, deep brain stimulation).

Eligible pharmacologic interventions included both FDA-approved medications for the treatment of a behavior disorder or management of disruptive behaviors in children and

medications used off-label for disruptive behavior. We identified specific pharmacologic agents from the following broad classes of drugs: alpha-agonists, anticonvulsants, second-generation (i.e., atypical) antipsychotics, beta-adrenergic blocking agents (i.e., beta-blockers), central nervous system stimulants, first-generation antipsychotics, selective serotonin reuptake inhibitors, mood stabilizers, and antihistamines.

We considered studies of a combined (i.e., co-administered, co-therapy, conjunctive, or adjunctive) intervention that included one or more of the eligible psychosocial or pharmacologic interventions identified in Key Questions 1-3 or was a uniquely described combination intervention designed or implemented specifically to treat children with disruptive behavior.

Outcomes

For Key Questions 1-4 and 6, eligible studies had to report at least one behavioral or functional outcome listed in the Analytic Framework (Figure 1). Studies had to report child outcomes to be considered for inclusion. We extracted information on long-term outcomes when they were reported. For Key Question 5, we included studies that reported harms (i.e., adverse effects) for an intervention included in Key Questions 1-4.

Timing

Eligible studies were not limited to intervention timing or duration of followup, but we limited the search to studies published in or after 1994. We conducted a preliminary screening of records retrieved from a search with no limits to the publication year. We screened approximately 1500 records published 20 or more years ago, and found that the study populations were inadequately described and poorly characterized, rendering a large number of the older studies unusable for this review. In order to include studies of patients meeting the population criteria for this review, the team agreed to limit the retrieval of primary study data to those studies published in or after 1994, as this date cutoff aligns with the availability of the *DSM-IV*.[16]

Setting

We focused on interventions in the clinical setting, including medical or psychosocial care delivered to individuals by clinical professionals, as well as individually focused programs to which clinicians refer patients. We excluded studies that were conducted exclusively in hospitalized participants (i.e., in-patients). We also excluded studies of a systems-level intervention (e.g., delivered universally in the school or juvenile detention setting).

Study Characteristics

We sought randomized controlled trials (RCTs) and nonrandomized controlled studies (i.e., prospective and retrospective cohort studies). We did not include case control studies as they are not an optimal study design for assessing causal inferences or measuring treatment effects. We did not include studies without comparators (e.g. case series) for the same reason.

For Key Questions 1-4, we sought original data from primary study publications. We identified and included data from related publications (i.e., publications reporting relevant outcomes from a study reported in a separate publication) if the primary study publication met inclusion criteria for the review. For Key Question 5, we included adverse events and harms data (for interventions identified in Key Questions 1-4) from studies, systematic reviews, and

regulatory reports to augment the harms data collected from the controlled prospective studies meeting the review inclusion criteria.

We did not specify a minimum sample size (i.e., number of participants per arm) for eligible studies. We restricted the review to studies published in English-language papers. TEP confirmed that key discipline specific publications from non-U.S. countries and international conferences present and publish material in English, minimizing the likelihood of language bias. However, we assessed abstracts from non-English language reports to assess the robustness of this assumption.

Data Extraction and Data Management

Data Extraction

We created data extraction forms to collect detailed information on the study characteristics, interventions, comparators, outcomes, outcome measures, and study quality and/or risk of bias (see Study Characteristics and Outcomes Data Files in the Systematic Review Data Repository). We enumerated the variables most important to this topic with input from Key Informants and Technical Experts and used the extraction forms to record participant characteristics, intervention characteristics, outcomes, and potential modifiers of treatment effects from each included study. The forms included detailed instructions and labels to reinforce coding reliability and consisted of items with mutually exclusive and exhaustive answer options to promote consistency. A senior level team member reviewed the data extraction against the original articles for quality control. The study and data abstraction forms were used to develop summary tables across selected groups of studies.

We recorded descriptive data for each study that met the full text screening criteria including study design, year, location, setting, randomization, blinding, elements of study quality, and related publications. We flagged related publications and extracted nonduplicate study data. We categorized location by country with the exception of Puerto Rico, which we categorized separately from the U.S. due to cultural differences in the study population. We recorded the source of funding and authors' competing interest disclosures for all studies included in the review.

We recorded intervention characteristics and components in detail, noting data elements not reported or unavailable from the primary or related study publications. We classified interventions according to their treatment components, specifically: 1) interventions including only a child component; 2) interventions including only a parent component; and 3) multicomponent interventions. Multicomponent interventions were defined as those that included two or more of a child component, parent component, or other component (e.g., teacher component, family together component).

We categorized outcomes broadly as behavioral or functional. We extracted information on how the outcome was measured and the outcome measurement time points. We include broad measures of quality of life and social functioning.

To assess the evidence on harms, we first collected adverse outcomes reported in studies included for effectiveness. We also identified the evidence for harms of pharmacologic interventions used to treat disruptive behavior reported in the gray literature, including integrated safety reports from the U.S. Food and Drug Administration's regulatory documents.

We recorded potential modifiers to determine whether specific variables affected treatment response. We anticipated that patient age and certain disorder characteristics (such as disease severity) would be robust predictors of outcomes.

We also extracted information on intervention delivery, intervention setting, and environmental factors (e.g., parental engagement) that may account for variations in observed treatment effects. The potential modifiers represent categories of variables that we anticipated may be linked to treatment effects. We extracted the reported variables from included studies and organized the information into meaningful groups to permit syntheses.

Data Management

We registered the review protocol (Registration #CRD42014007552) with PROSPERO, an international database of prospectively registered systematic reviews in health and social care. We used DistillerSR (Evidence Partners, Ottawa, Canada) for screening references. We tracked the literature search retrieval and screening results in EndNote. We used forms to extract the study data, and transferred the data to Excel. We deposited the data that were used in the meta-analyses into the Systematic Review Data Repository (SRDR) system.

Assessment of Methodological Risk of Bias of Individual Studies

We assessed the risk of bias of studies for behavioral outcomes of interest specified in the PICOTS (Table 1) according to the guidance in the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[70] Two senior investigators independently assessed each included study. Disagreements between assessors were resolved through discussion.

We used the Cochrane Risk of Bias Tool[71] (Appendix C) to assess risk of bias for randomized controlled trials (RCTs) of effectiveness. Reviewers rated six items from five domains of potential sources of bias (i.e., selection, reporting, performance, detection, and attrition) and one item for "other" sources of bias. We assessed for detection bias by evaluating outcome measurement and assessment methods to detect effects. We evaluated potential risk of bias associated with fidelity for psychosocial interventions and included those assessments in the category of "other bias." To assess risk of bias for study designs other than RCTs, we used the RTI Item Bank[72] for cohort studies (i.e., nonrandomized controlled trials) and the AMSTAR tool for systematic reviews and meta-analyses (Appendix C).[73-75] To assess the risk of bias associated with the reporting of harms, we used a four question modified tool adapted from the McMaster Assessment of Harms Tool (Appendix C).[76]

Determining Risk of Bias Ratings

We assigned studies an overall rating of "low," "moderate," or "high" risk of bias. We expected RCTs to receive positive assessments for questions about randomization, allocation concealment, and blinding in order to be designated "low risk of bias." We considered the feasibility of blinding in psychosocial studies and did not downgrade where it would have been impossible. Cohort studies that received positive scores on all items were assessed as "low risk of bias." Cohort studies with two or fewer negative ratings were assessed as "moderate risk of bias" and studies with more than two negative scores were assessed as "high risk of bias." We required that studies assessed for harms reporting receive a positive rating (i.e., affirmative response) on all four questions to receive a rating of "good." Studies with at least three positive

responses were considered “fair” quality and those with less than three positive responses were assessed as “poor” quality.

Data Synthesis

We examined the appropriateness of each study for inclusion in a meta-analysis. Studies that were too heterogeneous or otherwise unsuitable to contribute data to the meta-analysis were included as part of a narrative synthesis.

Qualitative Synthesis of Results

We qualitatively synthesized the literature based on the data extracted (described above) for each Key Question. We present behavioral outcomes (KQ1 and KQ2) and harms data (KQ5) in summary tables within the text. For the qualitative summary of KQ1, we organized the results by age (preschool, school age, and teenage) and characterized the studies as those that evaluated a child-only, a parent only, or a multicomponent intervention, based on the active treatment arm. We defined multicomponent interventions as those that included two or more of a child component, parent component, or other component (e.g., teacher component, family together component). We further grouped the summary of studies for KQ1 by named interventions (e.g., PCIT, Triple P, and Incredible Years) where possible. This categorization provided an organizational structure to characterize the literature and highlight key findings for similar interventions. For KQ2 we grouped the studies by individual pharmacologic agent or by pharmacologic class.

Quantitative Synthesis of Results

We developed a Bayesian multivariate, mixed treatment (network) meta-analysis to address the comparative effectiveness of psychosocial interventions for improving behavioral outcomes for children treated for disruptive behaviors (Key Question 1). We used Bayesian multivariate, mixed treatment (network) meta-analytic methods[77-79] to use both direct and indirect evidence for comparing a large suite of treatments. Network meta-analysis allows for a broader, integrated view of the available evidence, allowing for the relative merits of a set of treatments to be more readily compared. This approach borrows strength from indirect comparisons of interventions that have not been compared head-to-head in the same study. By combining direct and indirect evidence in the same framework, the resulting meta-analysis may be more robust, with more precise meta-estimates, than traditional meta-analyses. In the absence of network meta-analysis, we would have been compelled to construct a number of smaller, separate meta-analyses that would have been less powerful and less comprehensive, with more evidence excluded relative to a unified network meta-analysis. Further, our model was multivariate, in the sense that multiple outcome measures were considered simultaneously; this improves the analysis by recognizing that outcomes are correlated, estimating that correlation directly as part of the analysis. We present additional details of the meta-analysis methods in Appendix D.

Twenty-eight of the 66 studies included in the qualitative review in KQ1 met the additional criteria for inclusion in our meta-analysis. These additional criteria were that the study was an RCT that reported baseline and end-of-treatment means and standard deviations using one (or more) of the three most prevalent of the 16 instruments used in this literature to examine parent reported outcomes: (1) Eyberg Child Behavior Inventory (ECBI), Intensity Subscale; (2) ECBI, Problem Subscale; and (3) Child Behavior Checklist (CBCL), Externalizing (T-score) (see

Appendix E for a description of the instruments). Other instruments were not included in the analysis because of heterogeneity of constructs examined and an inadequate number of studies per measure.

To account for the large suite of interventions employed by the constituent studies, we classified the study arms of each included study according to their treatment components or as a control. Specifically, the treatment arms of each study were classified as one of the following types: (1) interventions including only a child component; (2) interventions including only a parent component; and (3) multicomponent interventions. Multicomponent interventions were defined as those that included two or more of a child component, parent component, or other component (e.g., teacher component, family together component). All interventions classified as multicomponent included a parent component. Study arms not identified by any of these three classes were defined as a control arm (i.e., waitlist control or treatment-as-usual arm). Recognizing that these treatment categories are broad, encompassing a range of specific interventions, each component was modeled as a random effect. This allowed for variation in treatment effect within each class, due to factors not explicitly modeled here. All measurement instruments shared the same study arm treatment effect in our model.

Studies were included in the meta-analysis if they reported baseline and end-of-treatment means and standard deviations from one of the three metrics listed above. The baseline was subtracted from the end-of-treatment mean and used as the response measure, along with the sum of their standard deviations. The three outcomes were modeled jointly as a multivariate normal likelihood, with any unmeasured outcomes treated as missing data; this allowed for the covariance among measures to be accounted for and estimated.

The age of subjects in each study arm was included in the model as a categorical covariate, broadly grouped into either prekindergarten, preteen child or teenage categories. The preteen child was used as the baseline value because it was the most prevalent among studies. The age covariate was combined additively with the intervention component effects and control/treatment-as-usual means to model the observed treatment differences relative to baseline. Though we considered age-by-treatment interactions, there was not enough balance among the age and treatment combinations to include them in the final model.

All unknown parameters were given weakly-informative prior distributions and estimated using Markov chain Monte Carlo[80] methods via the PyMC 2.3 software package.[81] The model was run for 200,000 iterations, with the first 150,000 samples conservatively discarded as burn-in, leaving 50,000 for inference.

Incorporating Existing Systematic Reviews

We located reviews published between 2005 and 2014 and evaluated each for relevance using the review PICOTS (Appendix B). We summarize review data from relevant psychosocial and pharmacologic interventions in the “Discussion” section of the report and in a table in Appendix F. For the systematic reviews reporting harms, we assessed quality using AMSTAR[73] and summarized the findings in KQ5.

Grading the Strength of Evidence

Strength of Evidence Assessments

We referenced the recommendations from the AHRQ EHC Methods Guidance and updated guidance for grading the strength of a body of evidence.[82,83] In accordance with the methods guidance, we first assessed and graded "domains" using established concepts of the quantity and quality of evidence, and coherence or consistency of findings. Two senior staff independently graded the body of evidence; disagreements were resolved through discussion.

We assessed strength of evidence for the direction or estimate of effect for the behavioral outcomes and interventions listed in Table 3.

Table 3. Selected outcomes and comparisons for the strength of evidence assessments

Outcome	Intervention	KQ
Change in disruptive behavior	Psychosocial Intervention	KQ1
• ECBI, Problem subscale • ECBI, Intensity subscale • CBCL, Externalizing score	Child only Parent only Mixed component	
Change in disruptive behavior or aggression	Pharmacologic Intervention	KQ2
• SDQ • OAS • CGI	Second generation antipsychotic Antiepileptic Medications used to ADHD	

ADHD = attention deficit hyperactivity disorder**;** CBCL = Child Behavior Checklist; CGI = Clinical Global Impressions; ECBI = Eyberg Child Behavior Inventory; KQ = Key Question; OAS = Overt Aggression Scale; SDQ = Strengths and Difficulties Questionnaire

We assessed an overall evidence grade based on the ratings for the following domains: study limitations; directness; consistency; precision; and reporting bias. We considered additional domains, as appropriate: dose-response association, plausible confounding, and strength of association (i.e., magnitude of effect). The fifth required domain, reporting bias, includes publication bias, selective outcome reporting, and selective analysis reporting.[82] To assess publication bias in the pharmacologic literature, we sought study protocols and data from regulatory sources and compared this information to the results in the published literature. The issue of publication bias in psychological science is difficult to address given the current lack of standards regarding the registration of study protocols in social sciences. We attempted to minimize the potential for bias introduced by the "file drawer effect" (i.e., nonpublication of studies with nonsignificant results) by expanding the literature search to include unpublished sources (e.g., meeting abstracts) and asking Key Informants about current research or developments in the field that may not yet be published.

Overall Strength of Evidence

We summarize the four grades (high, moderate, low, and insufficient) we used for the overall assessment of the body of evidence in Table 4 (adapted from the AHRQ "Methods Updated Guidance for Grading the Strength of a Body of Evidence"[82]). When no studies were available for an outcome or comparison of interest, we graded the evidence as insufficient.

Table 4. Strength of evidence grades and definitions[a]

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

[a] Excerpted from Berkman et al. 2013[84]

Assessing Applicability

We assessed the applicability of the findings to the population being treated for disruptive behavior disorders and the settings in which treatment occurs. We summarized common features of the study population and documented diagnoses. We considered patient age, intervention setting, treatment history, co-occurring diagnoses, and symptom severity reported in the included studies and the degree to which the populations studied reflect the target population for practice. As resource-poor environments may be limited in the options and types of interventions available, we characterized the resources needed including types of providers or involvement of nonclinical providers or families to implement effective interventions and provide the end users with adequate data on feasibility and implementation planning. We present applicability tables for each intervention in Appendix G.

Findings

Description of Included Studies

The PRISMA[85] literature flow diagram (Figure 2) reports the number of records retrieved from indexed, published literature and the overall number of records (including unique studies and related publications) retained for all Key Questions (KQs) and the meta-analysis. From our search of the literature we screened 7470 records; we excluded 6502 based on the abstract and title. We retrieved the full text of 968 publications. Of these, 852 were excluded for one or more reasons. Appendix H includes a list of excluded publications and exclusion reasons.

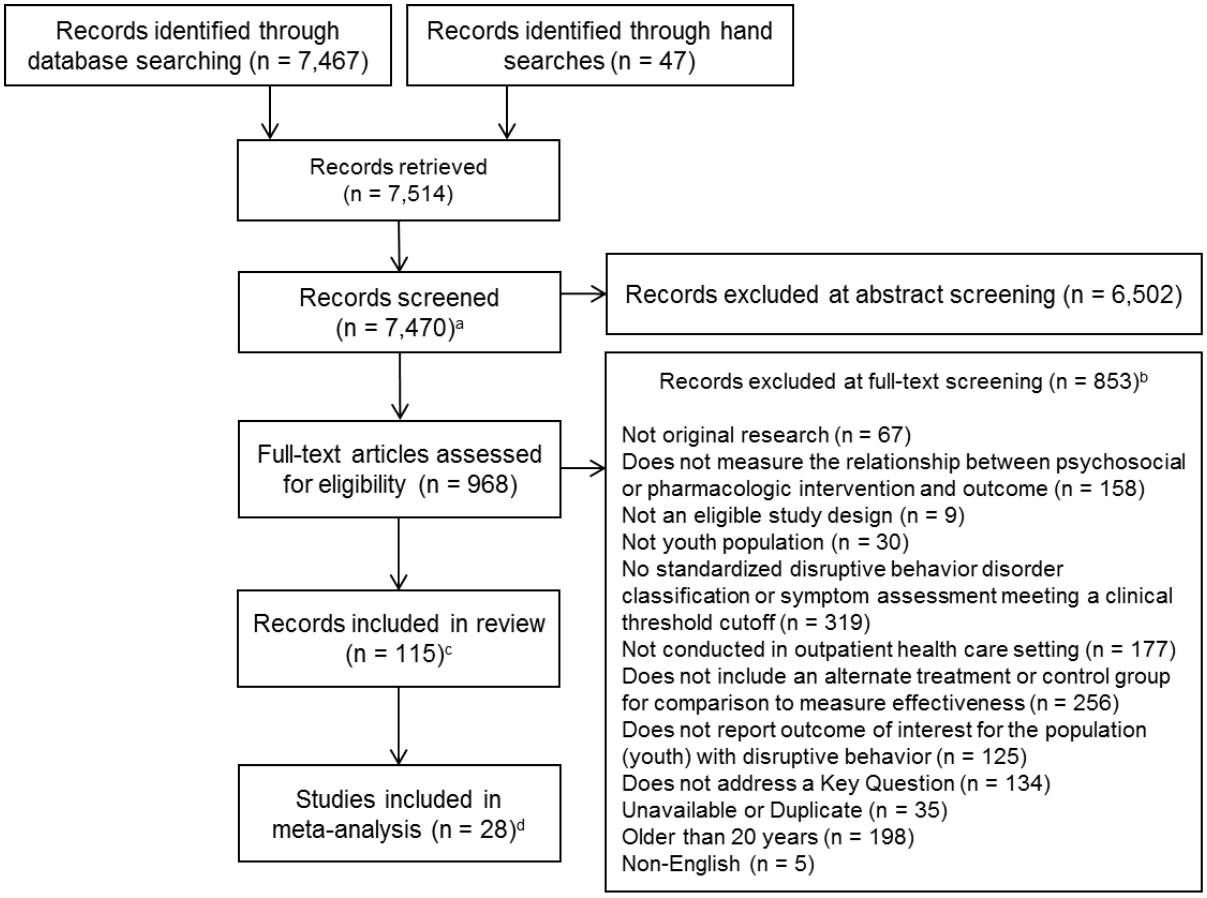
We retained 115 publications, representing 84 unique studies to address one or more KQs in this review. For Key Question 1 (KQ1) we identified 89 publications representing 66 unique studies. For Key Question 2 (KQ2) we identified 15 publications representing 13 unique studies. We included the data from the 13 studies addressing KQ2 and identified an additional three studies for Key Question 5 (KQ5). We found no head-to-head studies assessing the effectiveness of psychosocial versus pharmacologic intervention (Key Question 3) or combined psychosocial and pharmacologic interventions (Key Question 4) for the treatment of disruptive behavior in children. We summarize information on moderators and mediators of intervention effectiveness for Key Question 6 (KQ6) from 23 studies that addressed KQ1 or KQ2. For each KQ, we present findings by intervention and outcome where possible.

Studies of psychosocial interventions (KQ1) were heterogeneous. We categorized studies based on the active study arm and identified psychosocial interventions including only a child component, interventions including only a parent component, or as multicomponent (i.e., two or more of a child, parent, or other type of intervention component) intervention. We identified a subset of studies (n =28) from KQ1 to contribute data to the network meta-analysis. These studies were RCTs that reported baseline and end of treatment outcomes for at least one intervention and control group (i.e., study arm) using one or more of the three most prevalent measures of disruptive behavior (described above).

Pharmacologic interventions (KQ2) included antipsychotics, antiepileptics, and two groups of drugs (stimulants and nonstimulants) typically used to treat attention deficit hyperactivity disorder (ADHD). We report harms of pharmacologic interventions from 16 studies (reported in 18 papers). To augment the empirical data, we briefly summarized data from the gray literature (i.e., package inserts and FDA reviews) and prior systematic reviews (n = 3) that reported harms associated with the drugs that were included in the literature we assessed for KQ2. We compared the information obtained from the literature and regulatory sources with the Scientific Information Packets to confirm that we identified all relevant reports of harms data.

We present information reported in 37 publications (representing 23 studies) in KQ6 by patient characteristics (KQ6a), intervention characteristics (KQ6b), treatment history (KQ6c) and treatment characteristics (KQ6d).

Figure 2. Literature flow diagram



[a]Excluding discarded duplicates (n = 44).
[b]Records could be excluded for more than one reason.
[c]115 publications representing 84 unique studies.
[d]A subset of studies (n = 28) met eligibility criteria for inclusion in a quantitative analysis.

Key Question 1: In children under 18 years of age treated for disruptive behaviors, are any psychosocial interventions more effective for improving short-term and long-term psychosocial outcomes than no treatment or other psychosocial interventions?

Overview of the Literature for KQ1

This section presents results of studies meeting our review criteria and addressing the effectiveness of psychosocial treatments for disruptive behavior. Sixty-six studies (reported in 89 papers) of psychosocial intervention met the criteria for inclusion. Of the 66 included studies, 59 were randomized controlled trials (RCTs) (6031 was the total number of patients randomized for all studies in this section) and seven were nonrandomized controlled studies (including 1144 participants).[86-92] About half of the studies (n = 25) were conducted in the United States;[93-116] the remaining studies were conducted in: Australia (n = 11); Canada (n = 4); Germany (n = 3); Ireland (n = 2); Israel (n = 2); Netherlands (n = 5); Norway (n = 4); Puerto Rico (n = 1); Sweden (n = 3); and the United Kingdom (n = 5).[117-147] For the qualitative synthesis, we group studies by

active psychosocial intervention arm as interventions including only a child component, interventions including only a parent component, or as multicomponent interventions (Table 5). We defined a multicomponent intervention as one that included two or more of a child component, parent component, or other component (e.g., teacher component, family together component).

We report the findings first by age group (preschool age, school age, and teenage) and then by intervention, grouping first by components (e.g., child only, parent only, multicomponent) and then within components by specific interventions. We summarize the group difference in parent reported child disruptive behaviors reported by the Eyberg Child Behavior Inventory (ECBI) Intensity scale, ECBI Problem scale, or Child Behavior Checklist (CBCL) Externalizing scale T-score from baseline to the last followup in tables within each age group.

Table 5. Study characteristics (KQ1)

Characteristic		Preschool Age n = 23	School Age n = 29	Adolescent n = 14	All Ages
Study Design	RCT	22	24	13	59
	Cohort	1	5	1	7
Location	USA /Canada	10	13	6	29
	Europe	4	13	7	23
	Australia	8	2	0	11
	Other	1	1	1	3
Population Characteristics	Mean age, years	4.26	7.98	15.34	8.21
	Proportion males, %	68.25	77.73	71.40	72.94
	Randomized	2011	3585	1579	7175
	Analyzed[a]	1815	3019	1471	6305
Intervention Component	Child Only	0	1	1	2
	Parent Only	14	11	0	25
	Multiple components	9	17	13	39
Intervention	IY	5	7	0	12
	Triple P	5	0	0	5
	PCIT	7	0	0	7
	MST	0	0	5	5
	BSFT	0	0	3	3
	Other	6	22	6	34
Outcome Measure[b]	ECBI	20	10	1	31
	CBCL	8	15	8	31
	SDQ	2	4	0	6
	Observation	4	3	0	7
	Other	14	22	12	48
Risk of Bias (Quality)	High	10	9	5	24
	Moderate	11	18	5	34
	Low	2	2	4	8
	Total	**23**	**29**	**14**	**66**

BSFT = Brief Strategic Family Therapy; CBCL = Child Behavior Checklist; ECBI = Eyberg Child Behavior Inventory; IY = Incredible Years; KQ = Key Question; MST = Multisystemic Therapy; PCIT = Parent-Child Interaction Therapy; RCT = randomized, controlled trial; SDQ = Strengths and Difficulties Questionnaire

[a]Some studies do not report the number analyzed.

[b]Numbers do not tally as studies could use more than one measure.

The most commonly included named intervention was the Incredible Years (IY) program (12 studies). The IY program is a therapist-led, videotape modeling discussion program. The IY program includes child (IY-CT), parent (IY-PT), and teacher training (IY-TT) programs, which may be delivered individually or in combination with each other. The IY-PT program, for example, trains parents general ways of interacting and communicating with children and operant techniques for handling behavior problems.[148]

The next most commonly included named intervention was Parent Child Interaction Therapy (PCIT) (7 studies). PCIT is used primarily with young children with emotional and behavioral disorders emphasizes the quality of the parent-child relationship and parent-child interaction patterns.[149]

The third most commonly included named interventions (5 studies each) were the Positive Parenting Program (Triple P) and Multisystemic Therapy (MST). Triple P provides parenting and family support to prevent and treat behavioral and emotional problems in children and teenagers. The program uses a multilevel approach and draws on social learning, cognitive behavioral and developmental theory to teach parenting strategies to develop positive relationships, attitudes and conduct.[150] Multisystemic Therapy (MST) is family-based treatment approach for improving the antisocial behavior. MST is conducted in the youth's home, school, or community. The focus of MST is to teach parents how to be more effective at managing their child's activities and develop positive support systems.[151]

Brief Strategies Family Therapy (BSFT) was the active intervention in three included studies. BSFT is a short-term office-based model focused on the family to reduce mild to moderate behavior problems in adolescents.[152]

The 34 remaining included studies did not include more than two studies of any other named intervention. Interventions such as Parent Management Training Oregon Model (PMTO), the Coping Power Program, Helping the Noncompliant Child, and the Stop Now and Plan Under 12 Outreach Project (SNAP Under 12) program are representative examples.

Following the qualitative summary of the literature for KQ1, we report the findings from a Bayesian multivariate, mixed treatment (network) meta-analysis of a subset of the KQ1 literature (28 of 66 studies) that met criteria for inclusion in this analysis (as described in Methods above). For the network meta-analysis, we classified the active psychosocial intervention arm, active treatment comparison arms (if applicable), and control arms as interventions including only a child component, interventions including only a parent component, multicomponent interventions (as defined above), or as a control arm (also as defined above).

Key Points for KQ1

Preschool Children

- A majority (17 of 23) of studies of psychosocial interventions for preschool-age children with disruptive behaviors assessed one of three programs: IY (n = 5); PCIT (n = 7); and Triple P (n = 5). The six other studies assessed each assessed a different intervention.
- We categorized 14 studies as examining an intervention with an active treatment arm with only a parent component and nine studies as examining multicomponent interventions. There were no studies in this age group examining an intervention with only a child component as the active treatment.

- In three of five studies assessing only the parent-training component of the IY intervention, outcomes on the ECBI and CBCL were significantly improved in the treatment versus control arms. Outcomes did not differ between groups in two studies.
- In all five studies assessing the Triple P intervention, outcomes on the ECBI were significantly improved in the treatment compared with the control arms.
- In all seven studies assessing PCIT, problem behavior outcomes were significantly improved in the treatment group compared with the control arms. In the two studies comparing adapted versions of PCIT, differences in effects of PCIT versions were not significant.

School-Age Children

- Of the studies that assessed psychosocial interventions for school-age children with disruptive behaviors, the active treatment arm was categorized as including only a child component in 1 study, 11 studies as only a parent component, and 17 studies as multicomponent.
- Five of the 11 interventions identified as including only a parent component examined the parent training program of the IY-PT intervention (n = 3) or PMTO (n = 2). The six other studies each assessed a different intervention.
- Studies assessing IY-PT or PMTO interventions consistently reported greater improvements in child disruptive behaviors in the treatment versus control arms.
- A majority (10 of 17) of the studies examining multicomponent interventions assessed more than one of the IY intervention components delivered together (n = 4), the Coping Power Program (n = 2), a modular intervention (n = 2), or SNAP Under 12 ORP (n = 2). The seven other studies each assessed a different intervention.
- The IY and SNAP Under 12 ORP interventions consistently resulted in greater improvements in child disruptive behaviors than controls.

Teenage Children

- Of the studies that assessed psychosocial interventions for teenagers with disruptive behaviors, the active treatment arm of one study was categorized as including only a child component and of 13 studies to assess multicomponent interventions.
- A majority (8 of 14) of the studies examined one of two interventions: MST (n = 5) and BSFT (n = 3).
- Four of the five studies assessing MST reported significantly greater reductions in child disruptive behaviors for the treatment versus control arms.
- Each of the three studies assessing BSFT reported significantly greater reductions in child disruptive behavior compared with the control arms.

Meta-Analysis

- Results from our Bayesian multivariate, mixed treatment (network) meta-analysis indicated that the probability of having the largest effect was the same for multicomponent interventions (43%) and interventions with only a parent component (43%) , followed by interventions with only a child component (14%). All interventions categorized as multicomponent interventions included a parent component and at least one of a child, teacher, family together, or other component. Each of these intervention categories was associated with better outcomes than control arms.

Preschool Children

Description of Included Studies

We identified 23 studies[87,93,95,98,99,102,107,109,112,114,119,127,129,133,135,138-141,145,153-155] represented in 31 publications[87,93,95,98,99,102,107,109,112,119,127,129,133,135,138-141,145,153-163] that examined psychosocial interventions for preschool-age children with disruptive behaviors. Of the 23 included studies, 22 were RCTs (10 high, 10 moderate, and 2 low risk of bias)[93,95,98,99,102,107,109,112,114,119,127,133,135,138-141,145,153-155,158] and one was a prospective nonrandomized controlled study (moderate risk of bias).[87] Studies were conducted in the United States (n = 9)[93,95,98,99,102,107,109,112,114] and Australia (n = 9).[133,135,140,141,145,153-155,164] We identified a single study conducted in one of each country: Canada,[127] Ireland,[138] Israel,[119] the Netherlands,[87] and the United Kingdom.[129] Fourteen of the 23 included studies evaluated interventions including only a parent-component (Table 6). Nine of the 23 included studies evaluated multicomponent interventions. Each type of intervention is discussed separately below.

Table 6. Summary of interventions and risk of bias for studies of psychosocial interventions in preschool-age children with DBD

Intervention		High Risk of Bias	Moderate Risk of Bias	Low Risk of Bias	All
Parent Only					**14**
	IY-PT	1	3	1	5
	Triple P	2	3	-	5
	Other	2	2	-	4
Multicomponent					**9**
	PCIT	3	3	1	7
	Other	2	-	-	2
	Total	**10**	**11**	**2**	**23**

IY-PT = Incredible Years-Parent Training; PCIT = Parent-Child Interaction Therapy; Triple P = Positive Parenting Program

Detailed Analysis

Interventions With Only a Parent Component

Of the 14 studies evaluating interventions with only a parent component for preschool-age children with disruptive behaviors, we identified five studies[87,93,102,129,138] (reported in 8 publications)[87,93,102,129,138,158,159,163] that examined the Incredible Years– Parent Training (IY-PT) program. We identified five studies of Triple P,[135,139-141,145] and four RCTs that examined other interventions including only a parent component.[95,119,127,155]

Incredible Years – Parent Training (IY-PT)

Four RCTs (1 high, 2 moderate, and 1 low risk of bias)[93,102,129,138] and one prospective cohort study (moderate risk of bias)[87] evaluated a version of the IY-PT (Table 7). Of these, two RCTs[129,138] and the prospective cohort study[87] evaluated the standard version of the IY-PT, one RCT[93] evaluated a brief version of the IY-PT, and one RCT (reported in 2 publications)[102,159] evaluated a nurse-led or therapist-led version of the IY-PT.

Table 7. Summary of behavior outcomes from studies of a parent-only component (IY-PT) in preschool-age children

Author, Year Design (Risk of Bias) Country: N Randomized	Groups	Behavior Measure	Between-Group Difference[a]
Perrin et al., 2013[93] RCT (Moderate) United States: 150	**G1:** IY-PT **G2:** WLC	ECBI, Problem	**G1 vs. G2:** p<0.05
		ECBI, Intensity	**G1 vs. G2:** p<0.05
Posthumus et al., 2012[87] NRCT (Moderate) Netherlands: 144	**G1:** IY-PT **G2:** TAU	ECBI, Problem	**G1 vs. G2:** p=NS
		ECBI, Intensity	**G1 vs. G2:** p=NS
Lavigne et al., 2008[102] RCT (High) United States: 117	**G1:** PT (Nurse-led) **G2:** PT (Psychologist-led) **G3:** MIT	ECBI, Intensity	**G1 vs. G3:** p=NS **G2 vs. G3:** p=NS **G1 vs. G2:** p=NS
		CBCL, Externalizing	**G1 vs. G3:** p=NS **G2 vs. G3:** p=NS **G1 vs. G2:** p=NS
Hutchings et al., 2007[129] RCT (Moderate) United Kingdom: 153	**G1:** IY-PT **G2:** WLC	ECBI, Intensity	**G1 vs. G2:** p<0.05
		ECBI, Problem	**G1 vs. G2:** p<0.05
McGilloway et al., 2012[138] and 2014[163] RCT (Low) Ireland: 149	**G1:** IY-PT **G2:** WLC	ECBI, Intensity	**G1 vs. G2:** p<0.001
		ECBI, Problem	**G1 vs. G2:** p<0.001

NRCT = nonrandomized controlled trial; RCT = randomized controlled trial; IY = Incredible Years; PT = parent training; MIT = minimal intervention therapy; WLC = waitlist control; TAU = treatment as usual; ECBI = Eyberg Child Behavior Inventory; CBCL = Child Behavior Checklist; NS = nonsignificant; G = group; N = number

[a]The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

All three of the studies evaluating the IY-PT standard version measured child disruptive behaviors using the ECBI Problem scale.[87,129,138,163] Two of these studies also used the ECBI Intensity scale and Dyadic Parent-Child Interaction Coding System-Revised (DPICS-R) as additional measures of child disruptive behaviors.[87,138] One study used the Strengths and Difficulties Questionnaire (SDQ)[138] and one used the CBCL.[102,159] Comparison groups included usual care (n = 1),[87] waitlist control group (n = 3),[93,129,138] and a group led by a different provider or receiving no interventionist-led training (1 study reported in 2 publications).[102,159] Timing of the final followup ranged from 3 months to 2 years post-intervention across studies. Table 7 summarizes key outcomes. Briefly, in three of the five studies, the groups receiving IY intervention had significantly improved behavioral outcomes compared with control arms. In one study comparing differing administration of the IY intervention and in comparing IY to usual care, ECBI outcomes did not differ significantly among groups.

The moderate risk of bias prospective cohort study[87] compared outcomes in 4-year old children [mean age: 4.2 (3.11)] scoring at or above the 80th percentile on the aggressive behavior scale of the CBCL to outcomes in children receiving usual care. Parents of children [n = 72, mean age: 50.3 (3.11) months, mean CBCL aggressive behavior raw score: 21.99 (4.37)] in the intervention group received 18 2-hour IY sessions (BASIC and ADVANCE) focusing on identifying strategies for dealing with child behaviors. Children in the control group [n = 72, mean age: 51.3 (2.53) months, CBCL aggressive behavior mean raw score: 22.49 (4.69)]

received usual care. Groups differed significantly at baseline on age (control group 2 months older than intervention group, p=0.02), observed use of critical statements by parents (intervention group parents more critical than control, p=0.05), and observed conduct problems (more conduct problem in intervention group vs. control, p=0.004). Children did not differ at baseline on parent-rated measures. At final followup (2 years post-intervention), groups did not differ significantly on the ECBI. In observer coding (DPICS-R) of interactions, parents in the intervention group used significantly fewer critical statements than in the control group, and conduct problems decreased significantly in the intervention group compared with the control arm.

One RCT (reported in 2 publications)[129,158] compared an IY intervention delivered by center staff in social service centers for economically disadvantaged children in the United Kingdom with a waitlist control group. Children included in the study were seen at the centers and had ECBI Intensity scores of 127 or greater or problem scores of 11 or greater, and most had low socioeconomic status. Eighty-six of the 104 children randomized to the IY group [mean age: 46.4 (6.6) months] and 45 of the 47 randomized to the waitlist control group [mean age: 46.2 (4.2) months] completed the followup assessments at 6 months post-treatment. In intention-to-treat analyses, the outcomes on both ECBI scales (intensity scale effect size: 0.89, 95% CI: 0.54 to 1.24; problem scale effect size: 0.63, 95% CI: 0.28 to 0.98) and on the SDQ conduct problems (effect size: 0.33, 95% CI: −0.02 to 0.68) scale were significantly improved (p values <0.05) in the IY group compared with controls. Instances of deviant child behavior coded in observations were lower in the IY group but group but group differences were not significant (effect size: 0.21; 95% CI: −0.13 to 0.55). Scores on hyperactivity scales (Conners, SDQ) were also significantly lower in the IY group compared with control (p values <0.05), while scores on the SDQ overall deviance scale did not differ significantly between groups.

Another trial conducted in Irish community service centers enrolled 149 children between the ages of 32 and 88 months who were referred to health services organizations for problem behaviors and who scored above the clinical cut offs (127 for Intensity and 11 for problem scale) on a parent-rated ECBI.[138,163] The IY intervention was delivered by center staff. Ninety-five of the 103 children randomized to the IY group and 42 of 45 in the waitlist control group completed followup final assessments approximately 3 months after the end of treatment. In intention-to-treat analyses, the IY group improved significantly on both ECBI scales (p values <0.001) compared with the control arm (ECBI Intensity effect size: 0.70; 95% CI: 0.4 to 1.1; ECBI Problem subscale effect size: 0.75; 95% CI: 0.4 to 1.1). Scores on measures of hyperactivity, prosocial behavior, and emotional well-being were also significantly improved in the IY arm compared with control (p values <0.01). Child problem behaviors coded in observations also decreased significantly in the IY arm versus the control arm (effect size: 1.07, 95% CI: 0.6 to 1.6), but observations of positive child behavior did not differ significantly between groups. Investigators conducted observations with a subset of children in both groups. Intention-to-treat analyses of the children originally randomized to the IY-PT group at 12-month post-treatment followup assessment demonstrated that treatment effects were maintained from 6-month followup (e.g., end of treatment) to 12-month followup, although effect sizes were nominally – but not statistically significantly – smaller.[163]

A moderate risk of bias RCT[93] compared outcomes in three groups: an intervention group randomly allocated to 10 weeks of IY parent training [n = 89, mean age: 2.8 (0.61) years]; a non-randomly allocated group receiving the 10-week training [n = 123, mean age: 2.90 (0.63) years]; and a randomly allocated waitlist control group [n = 61, mean age: 2.7 (0.55) years].[93] All

children had Infant-Toddler Social Emotional Assessment Scale scores at or above the 80th percentile. Groups were similar at baseline; however, families in the non-random IY group included more minorities and were more likely to report lower socioeconomic status. Mean baseline T-scores on the ECBI Problem subscale ranged from 60.1 to 62.8 and from 58.3 to 59.2 on the ECBI Intensity scale. At the 12-month followup, outcomes on the ECBI Problem and Intensity subscales and the Parenting Scale were significantly improved in both the IY arms compared with the control group ($p<0.05$). Mean decreases in negative parenting, child disruptive behaviors, and negative parent-child interaction coded on the DPICS-R were greater in the IY groups compared with the control group and did not differ significantly between the IY groups.

Another high risk of bias RCT evaluated outcomes following 6 to 12-week IY programs led by primary care nurses (n = 49 children) or by psychologists (n = 37 children) and among a group of children whose parents received the *Incredible Years* book but no specific interventionist-led training (n = 31 children).[102,159] While the study enrolled 117 children, only 91 completed all assessments (77%). All children were between the ages of 3 and 6.11 years, and all had scores above the 90th percentile on the CBCL Externalizing scale and *DSM-IV* diagnoses of Oppositional Defiant Disorder (ODD). The mean baseline CBCL Externalizing score (SD) across groups was 70.7 (5.96) and mean ECBI Intensity score (SD) was 155.44 (27.41). Groups did not differ demographically or in comorbidities (27.4% with concomitant ADHD). At 12-months post-intervention, groups did not differ significantly on any ECBI or CBCL scale, though all groups improved from baseline. Scores on the ECBI were in the normal range for 23.1 percent of children across groups at followup and were in the normal range for 47.9 percent of children on the CBCL Externalizing scale. In equivalence testing, the combined interventionist-led groups and book-only group were equivalent at the 10 percent level (differing by <10% at post-treatment and the 12-month followup) on both scales, as were the nurse-led and psychologist-led groups. In dose-effect analyses, effects on both scales improved with increasing training sessions attended.

Positive Parenting Program (Triple P)

Five RCTs (2 high and 3 moderate risk of bias) evaluated a version of Triple P.[135,139-141,145] Two studies evaluated a self-directed version,[139,141] two studies evaluated an enhanced version,[135,140] and one study evaluated an online version (Table 8).[145] All RCTs of Triple P that met criteria for inclusion in this review were conducted in Australia, two in rural populations.

All five studies measured child disruptive behaviors with the ECBI Intensity and Problem subscales. Four of the five studies also used the Parent Daily Report (PDR),[135,139-141] one study also used the SDQ,[145] and only one study measured one of our protocol-defined functional outcomes.[140] The only study to use direct observation[145] did not use this measure for all participants. Total comparison groups included waitlist control groups (n = 4) and usual care or self-directed treatment (n = 2). The duration of treatment ranged from 8 to 11 weekly sessions. Timing of last followup was 4 months post-intervention in one study,[141] 6 months post-intervention in three studies[135,139,145] and 1 and 3 years post-intervention in one.[140,160,162] Table 8 summarizes key outcomes. Overall, ECBI outcomes and mean number of problem behaviors were improved in treatment arms compared with control.

Table 8. Summary of behavior outcomes from studies of a parent-only component (Triple P) in preschool-age children

Author, Year Design (Risk of Bias) Country: N Randomized	Group	Behavior Measure	Between-Group Difference[a]
Connell et al., 1997[141] RCT (High) Australia: 24	**G1:** Triple P (Self-directed family intervention) **G2:** WLC	ECBI, Intensity (mother report)	**G1 vs. G2:** p=0.0005
		ECBI, Intensity (father report)	**G1 vs. G2:** p=0.0005
		ECBI, Problem (mother report)	**G1 vs. G2:** p=0.0005
		ECBI, Problem (father report)	**G1 vs. G2:** p=0.0005
Markie-Dadds et al., 2006[135] RCT (Moderate) Australia: 41	**G1:** Triple P (Enhanced self-directed) **G2:** Triple P (Self-directed) **G3:** WLC	ECBI, Intensity	**G1 vs. G3:** p<0.001 **G2 vs. G3:** p<0.001 **G1 vs. G2:** p<0.01
		ECBI, Problem	**G1 vs. G3:** p<0.001 **G2 vs. G3:** p<0.001 **G1 vs. G2:** p<0.05
Markie-Dadds et al., 2006[139] RCT (Moderate) Australia: 63	**G1:** Triple P (Self- directed) **G2:** WLC	ECBI, Intensity	**G1 vs. G2:** p<0.01
		ECBI, Problem	**G1 vs. G2:** p<0.01
Sanders et al., 2000[140] RCT (Moderate) Australia: 305	**G1:** Triple P (Enhanced) **G2:** Triple P (Standard) **G3:** Triple P (Self-directed) **G4:** WLC	ECBI, Intensity (mother report)	**G1 vs. G4:** p<0.001 **G2 vs. G4:** p<0.001 **G3 vs. G4:** p<0.05 **G1 vs. G3:** p=NS **G2 vs. G3:** p=NS **G1 vs. G2:** p=NS
		ECBI, Intensity (father report)	**G1 vs. G4:** p<0.01 **G2 vs. G4:** p<0.01 **G3 vs. G4:** p<0.01 **G1 vs. G3:** p=NS **G2 vs. G3:** p=NS **G1 vs. G2:** p=NS
Sanders et al., 2012[145] RCT (High) Australia: 116	**G1**: Triple P (Online) **G2**: WLC	ECBI, Intensity	**G1 vs. G2:** p=0.000
		ECBI, Problem	**G1 vs. G2:** p=0.000

ECBI = Eyberg Child Behavior Inventory; RCT = randomized controlled trial; WLC = waitlist control; Triple P = Positive Parenting Program; N = number; G = group

[a]The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

Note: Effect favors G1 unless noted otherwise.

One RCT comparing a 10-week, self-directed iteration of Triple P implemented by parents in rural areas of Australia to a waitlist control group reported improvements in behavioral outcomes in the intervention group [n = 12, mean age: 49.33 (14.05) months] compared with control [n = 11, mean age: 53.18 (11.26) months].[141] Children were initially identified based on parent concern and interest in the study. Parents completed a *DSM-IV* diagnostic interview by phone to evaluate for the presence of ADHD (present in 5 intervention and 7 waitlist children), ODD (present in 8 intervention and 6 waitlist children), or conduct disorder (present in 1 treatment and 2 waitlist children). Intervention group parents received printed books and workbooks to work through each week and participated in weekly calls (mean duration of 20 minutes; range: 5 to 30 minutes) with a trained therapist to encourage problem-solving skills. At the end of the 10-week intervention, ECBI scores as rated by mothers and fathers were significantly improved in the intervention group compared with the control (p=0.0005). Mothers, but not fathers, also rated the number of problem behaviors as significantly improved (p=0.016) in the intervention group

compared with control. At post-treatment 33 percent of children in the intervention arm remained above the clinical cut-off (ECBI score=127) for disruptive behavior, compared with 100 percent remaining in the clinical range in the control arm. At followup of seven of 12 intervention groups 4 months after the end of intervention, post-treatment effects were maintained except for an increase in child problem behaviors that remained lower than the mean baseline level. At followup, three of seven children (43%) remained in the clinical range for disruptive behavior on the ECBI.

Another RCT in a rural population compared a similar self-directed version of Triple P plus weekly phone conferences [n = 14, mean age: 47.21 (10.19) months] with self-directed Triple P alone [n = 15, mean age: 47.27 (9.84) months] and with a waitlist control arm [n = 12, mean age: 46.17 (13.29) months].[135] Children had to have an ECBI Intensity score of ≥127 or problem score of ≥ 11 at baseline and parental concern about disruptive behavior. ECBI Problem and Intensity subscale scores and mean number of problem behaviors as rated by mothers were significantly improved in the treatment groups versus control, with significantly greater improvements in the self-directed plus phone arm compared with either other arm (all p values <0.01). Father-rated measures were not significantly different among groups. At followup 6 months after the end of treatment, effects were maintained for the intervention plus phone group and the intervention alone group, with continuing mother-reported improvements in the level of disruptive behaviors in the latter group. Almost 70 percent (69%, n = 9) of the intervention plus phone group and 57 percent (n = 8) of the intervention alone group showed reliable change on the ECBI Intensity scale at the 6-month followup.

Another RCT of self-directed Triple P [n = 32 at baseline, mean age: 42.91 (9.16) months] compared with a waitlist condition [n = 31 at baseline, mean age: 43.26 (9.10) months] reported similarly improved outcomes after the 10-week intervention in the treatment arm.[139] Children had to have ECBI Intensity scores of ≥127 or problem score of ≥11 at baseline and parental concern about disruptive behavior. Scores on the ECBI Intensity and problem scales and the mean number of problem behaviors reported by parents were significantly improved in the treatment group (n = 21 at analysis) compared with control (n = 22 at analysis) at post-treatment (all p values <0.01; significance maintained in intention-to-treat analyses). At followup of 13 children in the intervention group 6 months after the end of treatment, improvements in child behavior were maintained, and 23 percent of children (3/13) showed clinically reliable behavioral improvements.

One RCT (reported in multiple publications) evaluated three variations of Triple P in 3-year old children compared with a waitlist control group (n = 77): self-directed alone (n = 75); self-directed plus 10 hours of therapist-led skills training with observation and feedback (n = 77); and self-directed plus 14 hours of skills training that included training in partner support and observation and feedback (n = 76).[140,160,162] Families included in the study had at least one indicator of "family adversity," which included maternal depression, low socioeconomic status or low occupational prestige, relationship conflict, or single parent family, and all children [mean age: 3.4 (3.66)] scored in the clinical range on the ECBI Intensity (≥127) or problem (≥11) scales. Attrition over the course of the intervention was significant, with 30 percent (66/228) not completing either the post-intervention or 1-year followup assessments. Analyses of attrition indicated that negative affect ratings were higher among parents who did not complete the intervention and that mothers who did not complete the intervention were more likely to rate child behavior negatively. At followup after 15 weeks of intervention, children in the Triple P plus 14-hour training condition had improved outcomes on the ECBI compared with children in

the waitlist or self-directed alone conditions. Fathers of children in either of the conditions that included additional training reported fewer behavior problems compared with fathers of children in the waitlist arm. Fewer negative child behaviors were recorded in observations in both the additional training arms compared with the waitlist control (p values <0.05) in the 14-hour training arm compared with the self-directed arm (p<0.05). At the 12-month post-treatment followup, improvements in child behavior were maintained in the arms with additional training, but differences were not significant. Forty children in the 14-hour training arm, 56 in the 10-hour training arm, 32 in the self-directed only arm, and 21 in the waitlist arm had moved from the clinical range for disruptive behavior to the typical range on the ECBI (differences between all treatment groups and waitlist group significant at p<0.01; differences between the 14-hour and self-directed group significant at p<0.05; differences between the 10-hour arm and self-directed and 14-hour and 10-hour arm not significant). In a followup of 139 participants 3 years after the end of intervention,[160] children continued to improve on measures of problem behavior from baseline but differences among groups were not significant, nor were the numbers of children who met diagnostic criteria for disruptive behavior disorders (range 23.4 to 32% with DBD diagnoses across treatment groups). Teacher ratings of behavior problems also did not differ among groups, and all ratings were in the non-clinical range.

A sub-analysis of 87 children with ADHD included in this RCT[162] assigned to the 14-hour training arm (n = 26), the 10-hour arm (n = 29), or the waiting list (n = 32) had similar outcomes to those in the larger group, with significantly improved behaviors rated on the ECBI in children in the treatment arms compared with control at post-intervention. The mean number of problem behaviors was similarly lower in the treatment arms (all p values <0.05), and differences between the two treatment arms were not significant. Effects were maintained at the 1-year followup with no significant differences between treatment arms. At least 60 percent of children in each treatment arm met criteria for reliable change on the ECBI (p=NS) at the 1-year followup.

Finally, one RCT compared an online version of Triple P (n = 60) with internet use as usual (n = 56) among parents of children ages 2 to 9 [mean: 4.7 (1.76)] years with elevated ECBI scores.[145] As in the other studies of Triple P, problem behaviors on the ECBI were significantly reduced in the intervention group compared with control at the 6-month followup (ECBI Problem subscale effect size: 0.60; ECBI Intensity subscale effect size: 0.74). Overall SDQ ratings were not significantly different between groups, nor were observed child disruptive behaviors (effect size: 0.14). At least 60 percent of children in the treatment arms were considered clinically improved on the ECBI Problem (60%, n = 34/57) and Intensity subscales (65%, n = 34/52) at the post-treatment assessment compared with 29 (n = 14/49) and 17 (n = 8/46) percent in the control group (p=0.001).

Other Interventions With Only a Parent Component

Four RCTs conducted in the United States (high risk of bias),[95] Canada (high risk of bias),[127] Israel (moderate risk of bias),[119] and Australia (moderate risk of bias)[155] examined other interventions including only a parent component (Table 9).[95,119,127,155] All interventions targeted parent behaviors related to communication and discipline. One study incorporated technology to enhance the Helping the Noncompliant Child intervention,[95] one adapted parent-training modalities,[119] one evaluated Supportive Expressive Therapy-Parent Child model,[127] and one randomized children to group program for parents called Tuning into Kids (TIK).[155] Comparison groups included IY parent training, minimal intervention, standard, non-enhanced care, and treatment as usual. The final followup occurred at 6 months in one study,[155]12 months after the end of intervention in two studies,[119,127] and was not clearly reported in one.[95]

Table 9. Summary of behavior outcomes from studies of a parent-only component (other) in preschool-age children

Author, Year Design (Risk of Bias) Country: N Randomized	Groups	Behavior Measure	Between-Group Difference[a]
Jones et al, 2013[95] RCT (High) United States: 22	**G1:** HNC (technology enhanced) **G2:** HNC (standard)	ECBI, Problem	**G1 vs. G2:** 95% CI: −0.51 to 1.56
		ECBI, Intensity	**G1 vs. G2:** 95% CI: −0.13 to 2.05
Somech et al., 2012[119] RCT (Moderate) Israel: 209	**G1:** PT **G2:** WLC	ECBI, Intensity	**G1 vs. G2:** p<0.001
Cummings et al., 2008[127] RCT (High) Canada: 54	**G1:** SET-PC **G2:** IY-PT	ECBI, Intensity	**G1 vs. G2:** p=NS
		CBCL, Externalizing	**G1 vs. G2:** p=NS
Havighurst et al., 2013[155] RCT (Moderate) Australia: 63	**G1**: TIK **G2**: TAU	ECBI, Problem	**G1 vs. G2**: p=NS
		ECBI, Intensity	**G1 vs. G2**: p=NS

CBCL = Child Behavior Checklist; ECBI = Eyberg Child Behavior Inventory; G = group; HNC = Helping the Noncompliant Child; IY = Incredible Years; N = number; NS = nonsignificant; PT = parent training; RCT = randomized controlled trial; SET-PC = Supportive Expressive Therapy-Parent Child; TIK = Tuning into Kids

[a]The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

One RCT compared the standard, clinic-based Helping the Noncompliant Child program [n = 8, mean age: 5.75 (2.12) years], which emphasizes parental attention and positive parent-child communication and relationships, with a technology-enhanced version [n = 7, mean age: 5.57 (1.27) years] that included the standard clinic-based training plus smartphones to watch video training, complete skill surveys, and to record interactions for feedback.[95] Both groups were lower income and had ECBI scores in the clinical range (127 on the intensity scale or 11 on the problem scale), with higher intensity scores in the enhanced intervention group compared with standard intervention [148.86 (22.51) vs. 131.5 (2.87), p=NR]. At the end of intervention (timing of followup after the 8-10 intervention sessions per group not clear), scores on the ECBI Intensity and Problem scales favored the enhanced group versus the standard intervention group with between-group effect sizes of 0.99 (95% CI: −0.13 to 2.05) for intensity and 0.54 (95% CI: −0.51 to 1.56) for the problem scale. Pre-post effect sizes for each group were more than 1.0, and post-scores on both ECBI scales were in the normative range for children in the technology-enhanced arm. Post-scores on the ECBI Intensity scale, but not the problem scale, were in the normative range for the standard treatment group.

Another RCT evaluated an intervention program (Hitkashrut) combining elements of parent training models including parental self-regulation, involvement of fathers, parent-child communication skills, and behavior management compared with undefined minimal intervention.[119] Children were eligible for the study if they scored in the clinical or sub-clinical range on a teacher-rated SDQ. Behavior outcomes on the ECBI for children in the treatment arm (n = 140, mean age: 48.51 (7.35) months] were significantly improved (p<0.001, effect size: 0.76) at 1 month post-intervention compared with the control arm [n = 69, mean age: 48.62 (6.59) months]. At followup of 60 percent of participants (96 in intervention group, 29 in control) 1-year post-intervention, conduct problems were significantly reduced from baseline in the Hitkashrut arm (p<0.001) but not in the control group. The odds of reliable improvement in conduct problems were higher in children in the treatment arm than for those in the control arm

(OR=5.09; 95% CI: 2.14 to 12.11) as were the odds of greater improvement in conduct problems from baseline (OR=3.24; 95% CI: 1.30 to 8.02).

One RCT compared the Supportive Expressive Therapy – Parent Child model (n = 27) to the IY-PT program (n = 27).[127] Supportive Expressive Therapy entails recognizing and adapting dysfunctional parent responses and expectations for child behavior. Both interventions were conducted among children [mean age: 4.2 (0.96)] referred to an outpatient clinic for externalizing behavior disorders, and groups differed at baseline with significantly greater ECBI and CBCL-rated disruptive behaviors in the IY group compared with control (p=0.013). Outcomes at post-intervention among the 18 treatment group completers and 19 IY completers were improved from baseline in both groups with no significant group differences and mean within-groups effect sizes of 0.66 (0.65) and 1.06 (1.57), respectively (p=NS). Observed child negative behaviors decreased over time in both groups, but group differences were not significant. Seven children in the Supportive Expressive Therapy group and 10 in the IY group no longer met the cut-off for disruptive behaviors in the ECBI or CBCL (exact cut-off used not reported) at post-intervention (p=NS). Improvements in outcomes were maintained at the 1-year followup with no group differences. Eight children in the Supportive Expressive Therapy group and six in the IY group were functioning in the normative range at the 1-year followup (p=NS).

Lastly, one moderate risk of bias RCT compared Tuning into Kids (TIK), described as a 6-week long group program for parents of preschool children, against waitlist clinical treatment as usual control.[155] The study sample included 54 children (78% boys) with a mean age of 59.31 (7.38) months. All children had elevated scores on the parent-reported ECBI Intensity score at baseline, with a mean Intensity Score of 169.34 (2.99) in the intervention group and 165.99 (28.82) in the control group. At end of treatment, scores in both groups decreased to 141.26 (23.79) and 157.46 (31.30) for the intervention and TAU groups, respectively (although the group-by-time interaction was not statistically significant). Similar results were reported for the ECBI Problem score [intervention baseline: 23.14 (5.51), end of treatment: 16.86 (6.66); TAU group baseline: 21.00 (8.26), end of treatment: 20.27 (9.04)]. Teacher-rated behavior intensity and problems via the Sutter-Eyberg Student Behavior Inventory were not measured at the end of treatment. At 6-month followup and with two booster sessions after the initial 6-week intervention, mean parent-rated behavior intensity was 148.61 (32.25) and 148.69 (30.36) and behavior problems was 15.57 (9.44) and 16.25 (9.09) for the intervention and control groups, respectively. At 6-month followup, the mean teacher-rated behavior intensity were 101.12 (35.57) and 137.11 (55.39) and behavior problems were 3.94 (6.50) and 10.12 (9.78), for intervention and treatment as usual groups, respectively. The group-by-time interaction was not reported.

Multicomponent Interventions

Of the nine studies evaluating multicomponent interventions for preschool-age children with disruptive behaviors, seven examined PCIT[98,99,109,112,114,133,153] and two studies examined another multicomponent intervention.[107,154]

Parent Child Interaction Therapy (PCIT)

Seven RCTs (reported in 10 publications)[98,99,109,112,114,133,153,156,157,161] evaluated a version of PCIT (Table 10). PCIT focuses on improving parent-child interactions to improve disruptive behaviors and combines child-directed play therapy and parent training in behavior management. Studies were conducted in the United States[98,99,109,112,114,156,157] and Australia.[133,153,161] Five studies (3 high and 2 moderate risk of bias) evaluated a standard version of

PCIT.[98,109,112,114,153,156] One low risk of bias study evaluated a culturally modified version,[99,157] and one study (moderate risk of bias) evaluated an abbreviated version.[133,161] Comparison groups included treatment as usual, waitlist control, and alternate versions of PCIT. All of the RCTs measured child disruptive behaviors with the ECBI Intensity subscale and five used a version of the DPICS observation coding system. Five of seven studies also used the ECBI Problem subscale,[98,99,109,112,114] and three of the seven studies used the CBCL externalizing scale.[98,99,157] Last followup after the end of treatment ranged from 4 months to a mean of 15.90 months.

Table 10. Summary of behavior outcomes from studies of multicomponent intervention (PCIT) in preschool-age children

Author, Year Design (Risk of Bias) Country: N Randomized	Groups	Behavior Measure	Between-Group Difference[a]
Bagner et al., 2010[98] RCT (High) United States: 28	**G1:** PCIT **G2:** WLC	ECBI, Problem	**G1 vs. G2:** p=0.000
		ECBI, Intensity	**G1 vs. G2:** p=0.000
		CBCL, Externalizing	**G1 vs. G2:** p=0.000
		CBCL, Aggressive behavior	**G1 vs. G2:** p=0.000
McCabe et al., 2009[99] RCT (Low) United States: 58	**G1:** PCIT (standard) **G2:** PCIT (culturally adapted) **G3:** TAU	ECBI, Problem	**G1, G2 vs. G3:** p=NR
		ECBI, Intensity	**G1, G2 vs. G3:** p=NR
		CBCL, Externalizing	**G1, G2 vs. G3:** p=NR
Nixon et al., 2003[133] RCT (Moderate) Australia: 54	**G1:** PCIT (standard) **G2:** PCIT (abbreviated) **G3:** WLC	ECBI, Intensity (mother report)	**G1 vs. G3:** p<0.01 **G2 vs. G3:** p<0.001 **G1 vs. G2:** p=NS
		ECBI, Intensity (father report)	**G1 vs. G3:** p=NS **G2 vs. G3:** p<0.05 **G1 vs. G2:** p=NS
		CBCL, Externalizing	**G1 vs. G3**: p=NS **G2 vs. G3:** p=NS **G1 vs. G2:** p=NS
Schuhmann et al., 1998[109] RCT (Moderate) United States: 64	**G1:** PCIT (Immediate treatment) **G2:** WLC	ECBI, Problem (mother report)	**G1 vs. G2:** p<0.01
		ECBI, Problem (father report)	**G1 vs. G2:** p=NS
		ECBI, Intensity (mother report)	**G1 vs.G2:** p<0.01
		ECBI, Intensity (father report)	**G1 vs. G2:** p<0.05
Eyberg et al., 1995[112] RCT (High) United States: 50	**G1:** PCIT (Immediate treatment) **G2:** WLC	ECBI, Problem (mother report)	**G1 vs. G2:** p<0.00
		ECBI, Intensity (mother report)	**G1 vs. G2:** p<0.02
Nixon et al., 2001[153] RCT (High) Australia: 34	**G1**: PCIT **G2**: WLC	ECBI, Intensity	**G1 vs. G2:** p<0.01
Brestan et al., 1997[114] RCT (Moderate) United States: 30	**G1**: PCIT **G2**: WLC	ECBI, Problem (mother report)	**G1 vs. G2:** p=0.0001
		ECBI, Intensity (mother report)	**G1 vs. G2:** p=0.0001
		ECBI, Problem (father report)	**G1 vs. G2:** p=0.045
		ECBI, Intensity (father report)	**G1 vs. G2:** p=0.02

ECBI = Eyberg Child Behavior Inventory; RCT = randomized controlled trial; CBCL = Child Behavior Checklist; G = group; N = number; NS = nonsignificant; WLC = waitlist control; PCIT = Parent Child Interaction Therapy; TAU = treatment as usual
[a]The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

Five RCTs (3 high and 2 moderate risk of bias) compared standard PCIT intervention with a waitlist control group.[98,109,112,153] The first RCT assessed outcomes in children born premature and exhibiting externalizing behavior problems.[98,156] Most children were referred to the study by clinical personnel (6% were self-referrals by mothers), and children had to score above the clinically significant range on the CBCL (T-score ≥60) to participate. Fourteen children were randomized to immediate PCIT [mean age: 39.7 (14.2) months] and 14 to the waitlist [mean age: 36.5 (13.0) months]. At the end of treatment assessment (4 months), CBCL and ECBI scores were significantly improved for the PCIT group compared with control ($p<0.01$). Changes were considered clinically significant (meeting magnitude for reliable change and CBCL T-score <60) in all children in the PCIT group (n = 11 at end of treatment), and in four of 14 children in the waitlist arm. At followup of 10 children in the PCT group 8 months after treatment, eight children maintained clinically significant changes and nine demonstrated continued improvement in behaviors from baseline to the final followup.

Another high risk of bias RCT assessed standard PCIT therapy (n = 37 families) compared with a waitlist control group (n = 27 families) in children with ODD [mean age: 59.2 (12.4) months].[109] Sixty-six percent of the children in the study had concomitant ADHD and 22 percent had conduct disorder. Groups differed at baseline on parental IQ, with higher maternal and paternal IQs among parents in the PCIT group compared with control ($p<0.05$). At the end of intervention (mean 13 sessions over 4 months), scores on the ECBI Intensity and ECBI Problem scales were significantly improved among the 22 families remaining in the PCIT group compared with the 20 remaining in the control group ($p<0.05$). At 4 months after the end of intervention treatment gains in the PCIT group were maintained, but the study did not assess within- or between-group differences. An earlier paper[112] reporting preliminary data on 50 of the 64 families described in the aforementioned paper[109] also reported greater improvement in the PCIT group as compared to the waitlist control group on both ECBI scales.

A high risk of bias RCT conducted in Australia randomized families to PCIT or waitlist control.[153] The study sample consisted of 34 children with a mean age of 46.52 (6.83) months in the PCIT group and 46.76 (7.50) months in the waitlist control group. Children met diagnostic criteria for ODD and had a disruptive behavior for at least 6 months. Parents were self-referred to participate. Authors reported pre- and post-intervention symptoms measured by ECBI Intensity scale for the PCIT and waitlist control groups and 6-month post-treatment effects for the PCIT group. The mean ECBI Intensity scores from baseline to end of treatment decreased in both the PCIT [baseline: 166.58 (18.93), end of treatment: 125.24 (21.67)] and waitlist control groups [baseline: 173.82 (22.72), end of treatment = 148.35 (19.05)]. Importantly, the mean scores for the PCIT group were in the normal range at end of treatment but the waitlist control group was not (and the difference was statistically significant).

One moderate risk of bias RCT compared children assigned to receive PCIT or to a waitlist control group. The study sample consisted of 30 children with a mean age of 4.53 (0.90) years. Mother ratings from baseline to end of treatment showed greater decrease on the ECBI Intensity scale for the PCIT group [baseline mean: 173(29.5), end of treatment mean: 133(37.7)] as compared to the waitlist control group [baseline mean: 176 (30.2), end of treatment mean: 170 (36.0)] and the ECBI Problem scale [PCIT baseline mean: 23 (5.8), end of treatment mean: 11 (10.7); WLC baseline mean: 25 (5.4), end of treatment mean: 24 (7.5)]. Similar results are reported for the ECBI problem scale. Two RCTs reported on adapted versions of PCIT—one culturally adapted for Mexican-American children (low risk of bias)[99,157] and one adapted to include self-directed methods to abbreviate treatment (moderate risk of bias).[133,161] The first RCT

compared three conditions: standard PCIT [n = 19, mean age: 48.9 (92) months]; PCIT culturally adapted for Mexican-Americans by using cultural references and representations [n = 21; mean age (SD): 54.3(11.6 months]; and treatment as usual, which included cognitive-behavioral therapy (CBT) and family therapy [n = 18, mean age: 55.1 (15.3) months].[99,157] Children included in the study were being treated for behavior problems and had a score above the ECBI clinical cut point (more than 127 on Intensity or more than 11 on Problems scale). Overall, 57 percent of families (n = 33) completed the full course of treatment, and 93 percent (n = 54) completed the post-treatment assessments. At the immediate post-treatment assessment, problem behaviors measured on the ECBI and CBCL were significantly reduced in both the PCIT groups compared with treatment-as-usual, but differences between the PCIT arms were not significant. Children improved on the ECBI from baseline in all three groups (ECBI Intensity scale post-treatment effect sizes: 3.38 in adapted PCIT, 2.14 in PCIT, and 1.78 in control; ECBI Problem scale effect size: 2.84 for adapted PCIT, 1.96 for PCIT, and 1.78 for control). Effect sizes at post-treatment on the CBCL were similarly greater than 1 in the PCIT groups and 0.83 in the control group. Outcomes on observational measures of parent and child-led play and compliance were similarly significantly improved in the PCIT groups compared with control, but no different between PCIT arms. Immediately post-treatment, children in the PCIT groups were below the normative mean for behavior problems on the ECBI Intensity scale and CBCL Externalizing scale, and control children were below the clinical cut-offs. At long-term followup of an unstated number of participants at a mean of 15.90 (4.25) and range 6.58 to 24.47 months after the end of treatment, improvements in problem behaviors were largely maintained, with effect sizes on ECBI and CBCL scales ranging from 0.88 to 3.27 across groups and the largest effect sizes in the adapted PCIT group. Differences between groups were not significant in corrected comparisons at long-term followup, although in uncorrected comparisons, behavior outcomes in the adapted PCIT arm were significantly improved compared with the control arm and did not differ from the standard PCIT group.

The second RCT (moderate risk of bias) compared standard PCIT (n = 17 at analysis); an abbreviated version incorporating videotaped trainings (n = 20 at analysis); and a waitlist control group (n = 17 at analysis) in 54 children with a mean age of 46.75 (6.63) months.[133,161] Children in the study had to score in the clinical range (≥132) on the ECBI Intensity scale, meet *DSM-IV* criteria for ODD, and have been referred for treatment for disruptive behaviors of 6 months or longer duration. The standard PCIT intervention was delivered over 15.5 hours while the abbreviated version was delivered in 9.5 hours. Immediately post-treatment, mother-rated ECBI scores were significantly reduced in both PCIT arms (with no significant differences between the PCIT groups) compared with the waitlist control group ($p<0.01$). Mothers in the standard PCIT arm also rated problem behaviors in the home as significantly reduced post-treatment compared with the waitlist ($p<0.05$), but such differences were not seen in the abbreviated PCIT arm. Differences were only significant for father-reported ECBI scores between the abbreviated PCIT arm and the waitlist ($p<0.05$). Group differences on the CBCL were not significant, nor were reports of observations of child problem behaviors. In corrected comparisons, however, no comparisons of parent-rated measures were significant. Treatment gains were maintained at 6-month and 12-month post-treatment followup, with no significant differences between the PCIT groups. At a final, 2-year followup of 10 children in the standard PCIT group and an unstated number in the abbreviated group, group differences continued to be nonsignificant, and mean ECBI scores for all children were in the non-clinical range (mother-rated ECBI effect size: −0.24; father-rated ECBI effects size: −0.21). Fifty-six percent of children in the standard PCIT

arm and 68 percent in the abbreviated group continued to meet criteria for ODD, and 67 to 70 percent in each arm met reliable change criteria for reduction in mother-rated oppositional behavior (group differences not significant).

Other Multicomponent Interventions

Two RCTs (both high risk of bias)[107,154] evaluated a multicomponent intervention for the treatment of disruptive behavior in preschool-age children (Table 11).

Table 11. Summary of behavior outcomes in studies of other multicomponent interventions in preschool-age children

Author, Year Design (Risk of Bias) Country: N Randomized	Groups	Behavior Measure	Between-Group Difference[a]
Jouriles et al., 2001[107] RCT (High) United States: 36	**G1:** MFT **G2:** Comparison	CBCL, Externalizing	**G1 vs. G2:** p<0.05
Sanders et al., 2000[154] RCT (High) Australia: 47	**G1**: CBFI **G2**: BFI	CBCL, Total	**G1 vs. G2**: p=NS

BFI = behavioral family therapy intervention; CBCL = child behavior checklist; CBFI = cognitive behavior and behavioral family therapy intervention; G = group; MFT = Multigroup family therapy; NS = nonsignificant; RCT = randomized controlled trial

[a]The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

One multicomponent intervention RCT[107] evaluated child and maternal outcomes at five time points across 16 months for multiple child and parental interventions. Study participants were 36 children [mean age: 5.67 (1.88) years] with a DSM diagnosis of ODD or conduct disorder whose mothers had sought refuge in a battered women's shelter. Investigators randomly assigned mother-child subject pairs to the intervention group, which received weekly sessions following discharge from a women's shelter and continuing for 8 months. Children and mothers in the intervention group received individualized counseling; mothers also received training in child management skills. Comparison mother-child subject pairs were encouraged through monthly meetings or phone calls to use existing community or shelter services. Groups were similar at baseline for demographic variables and screening measures. Mean CBCL Externalizing scale score at baseline was 66.28 (10.00) in the treatment group compared with 65.56 (9.13) in the comparison group. The treatment group demonstrated a greater rate of decrease in parent reported disruptive behaviors at the third assessment. CBCL score differences between groups were not significant, but the rate of improvement of problems was greater among children in the intervention group compared with the control group. At the fifth assessment (ending the 16-months) the mean CBCL Externalizing scale score was 49.79 (9.17) in the treatment group and 58.59 (13.62) in the comparison group (p=NR). Children in the intervention group (n = NR) moved into the normative range [i.e., less than one standard deviation above the mean CBCL Externalizing T-score for normative group of 50 (10)] on the CBCL Externalizing scale. Control children remained in the clinical range. By the final assessment, 3 of 18 children in the intervention group and 8 of 18 in the control group (p<0.05) had externalizing problems at clinical levels (vs. 13/18 in each group at baseline).

In a second RCT,[154] parents were randomized to behavioral family therapy intervention (BFI) or an enhanced group receiving cognitive therapy in addition to the family behavior therapy

intervention (CBFI). Both interventions are described as involving both parents and children, although parents are also described as the primary focus of each intervention. Both interventions include teaching a range of positive parenting techniques and strategies for managing misbehavior. The CBFI intervention also includes cognitive therapy components to treat maternal depression. The study sample included 47 families (mean age of children at intake: 4.39 years). All children were diagnosed with either conduct disorder or ODD either alone or in combination with ADHD. There were no significant group-by-time interactions for any parent-reported (CBCL, PDR) or observational measure (Family Observation Schedule), although significant main effects for time were reported for parent reports of child disruptive behavior via CBCL and PDR measures.

Summary of Key Disruptive Behavior Outcomes

We report the behavior outcomes measured by ECBI (Table 12) and CBCL (Table 13) from studies of preschool-age children.

Table 12. Summary of behavior outcomes reported by ECBI for preschool-age participants

Author (Year) Study Design (Risk of Bias)	Groups Analyzed (N)	Scale	Baseline Mean (SD)	Last Followup Mean (SD)	Between-Group Difference[a]
Bagner et al., 2010[98] RCT (High)	**G1:** PCIT (11) **G2:** WLC (14)	ECBI, Problem	**G1:** 61.8 (9.3) **G2:** 65.1 (7.9)	4 months post-baseline **G1:** 45.6 (5.5) **G2:** 61.1 (10.8)	p=0.000
		ECBI, Intensity	**G1:** 63.4 (12.2) **G2:** 64.1 (8.1)	4 months post-baseline **G1:** 43.0 (4.3) **G2:** 64.6 (9.5)	p=0.000
Nixon et al., 2003[133] RCT (Moderate)	**G1:** PCIT (Standard) (17) **G2:** PCIT (Abbreviated) (20) **G3:** WLC (NA)	ECBI, Intensity, (mother report)	**G1:** 166.6 (18.9) **G2:** 156.3 (16.8) **G3:** 173.8 (22.7)	6 months post-intervention **G1:** 117.5 (31.7) **G2:** 126.1 (18.0) **G3:** NA	p=NS
		ECBI, Intensity, (father report)	**G1:** 148.3 (24.5) **G2:** 139.1 (23.2) **G3:** 147.5 (26.0)	6 months post-intervention **G1:** 120.8 (23.7) **G2:** 115.5 (21.3) **G3:** NA	p=NS
Perrin et al., 2013[93] RCT (Moderate)	**G1:** IY-PT (89) **G2:** WLC (61)	ECBI, Problem	**G1:** 60.3 (NR) **G2:** 60.7 (NR)	12 months post-intervention **G1:** 51.7 (NR) **G2:** 59.7 (NR)	-0.6 (95% CI: −0.95 to −0.2), p<0.05
		ECBI, Intensity	**G1:** 58.9 (NR) **G2:** 59 (NR)	12 months post-intervention **G1:** 54.8 (NR) **G2:** 58.8 (NR)	ES= −0.43 (95% CI: −0.79 to −0.07), p<0.05
Jones et al, 2013[95] RCT (High)	**G1:** HNC (technology enhanced) (7) **G2:** HNC (standard) (8)	ECBI, Problem	**G1:** 22.6 (5.2) **G2:** 20.5 (4.8)	2 weeks post-intervention **G1:** 6.14 (5.7) **G2:** 8.88 (8.2)	ES=0.54 (95% CI: −0.5 to 1.6), p=NS
		ECBI, Intensity	**G1:** 148.9 (22.5) **G2:** 131.5 (23.9)	2 weeks post-intervention **G1:** 83 (15.3) **G2:** 91.6 (21.3)	ES=0.99 (95% CI: −0.1 to 2.1), p=NS
Somech et al., 2012[119] RCT (Moderate)	**G1:** PT (96) **G2:** WLC (29)	ECBI, Intensity	**G1:** 87.9 (10.5) **G2:** 88.3 (13.3)	12 months **G1:** 79.8 (12.0) **G2:** 86.7 (17.0)	OR=3.24 (95% CI: 1.3 to 8.02)

Table 12. Summary of behavior outcomes reported by ECBI for preschool-age participants (continued)

Author (Year) Study Design (Risk of Bias)	Groups Analyzed (N)	Scale	Baseline Mean (SD)	Last Followup Mean (SD)	Between-Group Difference[a]
Cummings et al., 2008[127] RCT (High)	**G1:** SET-PC (16) **G2:** IYPP (16)	ECBI, Intensity (T-score)	**G1:** 62.5 (4.6) **G2:** 67.5 (6.7)	12 months post-intervention **G1:** 59.2 (6.6) **G2:** 59.5 (9.1)	p=NS
Lavigne et al., 2008[102] RCT (High)	**G1:** PT (Nurse- led) (33) **G2:** PT (Psychologist-led) (33) **G3:** MIT (33)	ECBI, Intensity	**G1** + **G2** + **G3:** 155.4 (27.4)	12 months post-intervention (*reported as change from baseline*) **G1:** 17.2 **G2:** 28.6 **G3:** 19.1	p=NS
Nixon et al., 2014[153] RCT (High)	**G1**: PCIT (17) **G2**: WLC (17)	ECBI, Intensity	**G1**: 166.58 (18.93) **G2**: 173.82 (22.72)	6 month post-intervention **G1**: 117.47 (31.69) **G2**: NA	NR

BL = baseline; CI = confidence interval; ECBI = Eyberg Child Behavior Inventory; ES = effect size; G = group; IYPP = Incredible Years Parenting Program; IY-PT = Incredible Years Parent Training; MIT = minimal intervention; PT = parent training; N = number; NA = not applicable; NR = not reported; NS = not significant; OR = odds ratio; PCIT = Parent Child Interaction Therapy RCT = randomized controlled trial; SD = standard deviation; SET-PC = Supportive Expressive Therapy-Parent Child; WLC = waitlist control; TE-HNC = Technology Enhanced Helping the Noncompliant Child
[a]The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

Table 13. Summary of behavior outcomes reported by CBCL for preschool-age participants

Author, Year Design (Risk of Bias)	Groups Analyzed (N)	Scale	Baseline Mean (SD)	Last Followup Mean (SD)	Between-Group Difference[a]
Bagner et al., 2010[98] RCT (High)	**G1:** PCIT (11) **G2:** WLC (14)	CBCL, Aggressive Behavior	**G1:** 70.1 (10.9) **G2:** 75.8 (11.1)	4 months post-baseline **G1:** 51.1 (1.6) **G2:** 67.7 (10.2)	p=0.000
		CBCL, Externalizing	**G1:** 69.4 (9.1) **G2:** 74.2 (8.9)	4 months post-baseline **G1:** 47.9 (6.1) **G2:** 66.9 (8.4)	p=0.000
Nixon et al., 2003[133] RCT (High)	**G1:** PCIT (standard) (17) **G2:** PCIT (abbreviated) (20) **G3:** WLC (NA)	CBCL, Externalizing	**G1:** 25.82 (5.22) **G2:** 25.2 (7.33) **G3:** 26.24 (6.26)	6 months post-intervention **G1:** 15.24 (7.77) **G2:** 15.9 (7.33) **G3:** NA	p=NS
Cummings et al., 2008[127] RCT (High)	**G1:** SET-PC (16) **G2:** IYPP (16)	CBCL, Externalizing (T-score)	**G1:** 65 (4.64) **G2:** 69.89 (7.77)	12 months post-intervention **G1:** 57.81 (6.17) **G2:** 59.50 (9.62	p=NS
Lavigne et al., 2008[102] RCT (High)	**G1:** PT-Nurse led (33) **G2:** PT-Psychologist led (33) **G3:** MIT (33)	CBCL, Externalizing (T-score)	**G1 + G2 + G3:** 70.7 (5.96)	12 months post-intervention **G1 + G2 + G3:** NR	p=NS

Table 13. Summary of behavior outcomes reported by CBCL for preschool-age participants (continued)

Author, Year Design (Risk of Bias)	Groups Analyzed (N)	Scale	Baseline Mean (SD)	Last Followup Mean (SD)	Between-Group Difference[a]
Jouriles et al., 2001[107] RCT (High)	**G1:** MFT (18) **G2:** Comparison (18)	CBCL, Externalizing	**G1:** 66.28 (10) **G2:** 65.56 (9.13)	16 months post-intervention **G1:** 49.79 (9.17) **G2:** 58.59 (13.62)	p<0.05
McCabe et al., 2009[99] and McCabe et al., 2012[157] RCT (Low)	**G1:** GANA (20) **G2:** PCIT (15) **G3:** TAU (13)	CBCL, Externalizing	**G1:** 66.95 (8.95) **G2:** 67.21 (11.99) **G3:** 69.22 (12.27)	6 to 24 months post-intervention **G1:** 49.6 (9.01) **G2:** 53.33 (13.47) **G3:** 57.46 (14.44)	**G1 vs. G3:** p=0.04 **G1 vs. G2**: p=NS **G2 vs. G3**: p=NS
Sanders et al., 2000[154] RCT (High)	**G1**: CBFI **G2**: BFI	CBCL, Total	**G1:** 58.11 (9.74) **G2:** 66.78 (7.46)	6 months post-intervention **G1:** 60.21 (12.70) **G2:** 67.63 (10.63)	**G1 vs. G2:** p=NS

CBCL = Child Behavior Checklist; GANA = Guiando a Ninnos Activo; G = group; IYPP = Incredible Years Parenting Program; IYP = Incredible Years Program; MFT = Multigroup Family Therapy; MIT = minimal intervention; PT = parent training; N = number; NA = not applicable; NR = not reported; NS = not significant; PCIT = Parent Child Interaction Therapy; RCT = randomized controlled trial; SD = standard deviation; SET-PC = Supportive Expressive Therapy-Parent Child; TAU = treatment as usual; WLC = waitlist control

[a]The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

School-Age Children

Description of Included Studies

Twenty-nine studies identified as examining psychosocial interventions for school-age children with disruptive behaviors represented in 38 papers. Of the 29 studies, 24 were RCTs[96,97,100,101,103,105,108,110,113,117,118,121-123,125,126,128,130-132,134,137,147,165] and five were non-RCTs.[88-92] The RCTs were conducted in the United States (n = 9),[96,97,100,101,103,105,108,110,113] Norway (n = 4),[117,125,126,131] the United Kingdom (n = 3),[123,130,147] Canada (n = 2),[121,137] Sweden (n = 2),[118,122] the Netherlands (n = 2),[128,132] Australia (n = 1),[165] and Puerto Rico (n = 1).[134] Of the non-RCTs, studies, one each was conducted in the United States,[90] Australia,[91] Ireland,[88] Italy,[92] and Canada.[89] We assessed risk of bias as high for nine studies;[88-91,100,117,118,134,165] moderate in 18 studies; [92,96,97,101,103,105,108,110,113,122,125,126,128,130-132,137,147] and low for two studies[121,123] (Table 14).

Interventions were categorized as including only a child component (n = 1),[132] only a parent component (n = 11),[88,90,91,113,117,118,121,122,125,130,147] or as multicomponent interventions (n = 17).[89,92,96,97,100,101,103,105,108,110,123,126,128,131,134,137,165]

Table 14. Summary of interventions and risk of bias for studies of psychosocial interventions in school-age children with DBD

Intervention		High Risk of Bias	Moderate Risk of Bias	Low Risk of Bias	All
Single Component					12
	Child only	-	1	-	1
	Parent only	5	5	1	11
Multicomponent					17
	IY	-	4	-	4
	Coping Power	1	1	-	2
	Modular	-	2	-	2
	SNAP ORP	1	1	-	2
	Other	2	4	1	7
	Total	**9**	**18**	**2**	**29**

IY = Incredible Years; SNAP ORP = Stop Now and Plan Under 12 Outreach Project

Detailed Analysis

Interventions With Only a Child Component

We included one study (moderate risk of bias) examining interventions with only a child component for school-age children.[132] Overall, there was a statistically significant positive result for at least one behavioral outcome[132] and one statistically significant positive result for a functional outcome.[132] The study included parent-reports of child disruptive behaviors as measured by the CBCL Externalizing subscale and teacher-report (TRF) of child disruptive behaviors.[132] Investigators randomly assigned 97 aggressive Dutch boys [mean age: 11.2 (0.93) years] to receive a social cognitive intervention program (SCIP), social skills training (SST), or to a waitlist control group.[132] From baseline to post-treatment (11 weeks), there was a significant main effect for time for parent-reported child disruptive behaviors as measured by the CBCL Externalizing subscale [SCIP baseline mean: 66.78 (9.54), SCIP post-treatment mean: 63.31 (10.75); SST baseline mean: 69.73 (6.55), SST post-treatment mean: 61.60 (8.41); WLC baseline mean: 68.29 (5.88), WLC post-treatment mean: 63.71 (7.06)] but not significant effects of the intervention. Significant time by group interactions favoring SCIP were reported for most of these other variables when comparing children treated with SCIP versus SST.

Interventions With Only a Parent Component

Of the 11 studies examining interventions with only a parent component,[88,90,91,113,117,118,121,122,125,130,147] eight were RCTs[117,121,122,125,147,160,166,167] and three of the studies were non-RCTs.[88,90,91] Of the RCTs, two were rated high,[117,118] five were moderate[113,122,125,130,147] and one study was assessed as low[121] risk of bias. The most commonly examined behavioral outcome was general disruptive behavior as measured by parent report using one or more of the CBCL Externalizing scale (n = 4),[90,117,125,147,166,167] ECBI Problem subscale,[117,122,147,160,167] ECBI Intensity subscale,[117,122,147,160,167] SDQ,[88,91] or PDR;[122,125,160,166] the most commonly used teacher report measure was the TRF externalizing scale.[117,125,166] All but one study included at least one of these measures, with the remaining study examining the disruptive behaviors as the percentage of children meeting formal diagnostic criteria for a disruptive behavior disorder using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS).[121] four studies included functional outcomes, with the most

commonly examined being child social skills as measured by the Social Skills Rating System,[117,125,166] SCS,[122] or the Sutter-Eyberg Student Behavior Inventory (SESBI).[160]

Of the eight studies that measured general disruptive behavior with one or more parent report measure (e.g., CBCL Externalizing, ECBI Intensity, ECBI Problem, or SDQ), each measured a different active treatment. One compared the Parents Plus Children's Programme to treatment as usual and reported that in comparison to treatment as usual the treatment group displayed significant reductions in conduct problems as measured by the SDQ over 8-weeks of active treatment and at 5-month followup.[88] One study compared a Skilled Parenting group to a Perceptive Parenting group and reported reductions in conduct problems as measured by the SDQ in both treatment groups but greater reductions in the Skilled Parenting group over 8 weeks of active treatment.[91] One study compared a practitioner-directed parent management training program with a self-directed parent management training program and waitlist control group and reported that the practitioner-directed group and the self-directed group were superior to waitlist control group and that the practitioner-directed group was superior to the self-directed group from pre- to post-treatment and at 6-month followup.[122] One study compared the Helping the Noncompliant Child intervention to treatment as usual and reported no difference in disruptive behavior improvement between treatment conditions.[90] One study compared Parent Management Training – Oregon Model (PMTO) to treatment as usual and reported that PMTO was more effective than treatment as usual from pre- to post-treatment and at one-year followup.[125,166] One study compared a brief version of PMTO to treatment-as-usual and reported that brief-PMTO was more effective than treatment-as-usual from pre- to post-treatment.[117] One study compared a standard parent-training program to a more intensive version and reported that both treatments showed improvement from pre- to post-treatment but that the intensive version maintained more improvement at 4-year followup.[147,167]

The one study that measured child disruptive behavior by the proportion of children [mean age: 7.61 (2.62)] meeting formal diagnostic criteria for a disruptive behavior disorder on the KSADS, compared the Strongest Families intervention to treatment as usual and reported that significantly fewer children in the active treatment group met formal diagnostic criteria for ODD than in the treatment as usual group at 240- and 365-days post-randomization.[121]

Incredible Years – Parent Training (IY-PT)

Three RCTs (1 high and 2 moderate risk of bias) evaluated a version of the IY-PT (Table 15). Two studies examined IY-PT compared to a waitlist control;[118,130] one study examined IY-PT + ADVANCE compared to the standard IY-PT program.[113] All three studies measured child disruptive behaviors using the ECBI Problem subscale, and two studies also used the ECBI Intensity subscale[118,130] and direct observation of child behaviors (but different behavioral observation coding strategies),[113,130] and one study used each of the Sutter-Eyberg Child Behavior Inventory-Revised, Intensity subscale,[118] the SDQ,[118] and CBCL subscales.[113]

Table 15. Summary of behavior outcomes for studies of parent-only intervention (IY-PT) in school-age children

Author, Year Design (Risk of Bias) Country: N Randomized	Groups	Behavior Measure	Between-Group Difference[a]
Axberg et al., 2012[118] RCT (High) Sweden: 62	**G1**: IY-PT **G2**: WLC	ECBI, Problem	**G1 vs. G2:** p=0.003
		ECBI, Intensity	**G1 vs. G2:** p=0.001
Gardner et al., 2006[130] RCT (Moderate) United Kingdom: 76	**G1:** IY-PT **G2:** WLC	ECBI, Problem	**G1 vs. G2:** p=0.05
		ECBI, Intensity	**G1 vs. G2:** p=0.01
Webster-Stratton et al., 1994[113] RCT (Moderate) United States: 85	**G1:** IY-PT (ADVANCE) **G2:** IY-PT (basic)	CBCL, Total problems (mother report)	**G1 vs. G2:** p=NS
		CBCL, Total problems (father report)	**G1 vs. G2:** p=NS
		ECBI, Problem	**G1 vs. G2:** p=NS

CBCL = Child Behavior Checklist; ECBI = Eyberg Child Behavior Inventory; IY-PT = Incredible Years-Parent Training; G = group; N = number; NS = not significant; RCT = randomized controlled trial; WLC = waitlist control

[a]The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

An RCT conducted in Sweden examined 4 to 8 year old children (85% boys) referred for outpatient child and adolescent psychiatry services meeting diagnostic criteria for ODD. Patients were randomized to IY-PT or waitlist control group.[118] From baseline to the end of active treatment the children randomized to the IY-PT group showed significantly more improvement on the parent reported ECBI Intensity subscale [baseline mean: 160.0 (20.3); end of active treatment mean: 128.6 (26.5); change: 20% reduction] and Problem subscale [baseline mean: 20.83 (4.17); end of active treatment mean: 11.13 (7.85); change: 47% reduction] than did children in the waitlist control group [ECBI-I baseline mean: 152.9 (23.6); ECBI-I end of active treatment mean: 147.1 (26.0); change: 4%; ECBI-P baseline mean: 20.41 (6.58); ECBI-P end of active treatment mean: 17.53 (8.01); change: 14% reduction]. Significant differences were not reported on the SECBI-R Intensity subscale or the SDQ.

An RCT conducted in the United Kingdom examined 2 to 9 year old children (74% boys) referred to outpatient services for conduct problems and scoring above the clinical cutoff on the ECBI Problem subscale.[130] Children receiving IY-PT experienced greater reductions from baseline to post-intervention (14 weeks) on the ECBI Problem subscale [baseline mean: 20.8 (6.5), post-intervention mean: 12.4 (7.8); change: 40% reduction] ECBI Intensity subscale [baseline mean: 152.7 (39.2), post-intervention mean: 130.7 (29.9), change: 14% reduction], and negative behaviors as measured by direct observation [baseline mean: 58.5 (50.6), post-intervention mean: 30.3 (28.6), change: 48% reduction] as compared to children referred to a waitlist control group [ECBI-P baseline mean: 20.3 (7.0), ECBI-P post-intervention mean: 16.3 (8.6), change: 20% reduction; ECBI-I baseline mean: 156.1 (32.9), ECBI-I post-intervention mean: 148.5 (34.7), change: 5% reduction; observed negative behavior baseline mean: 39.9 (37.0), observed negative behavior post-intervention mean: 35.5 (31.5), change: 11% reduction).

One RCT conducted in the United States randomized 3 to 8 year old children (74% boys) scoring above the clinical cutoff on the ECBI, and meeting diagnostic criteria for ODD to receive either IY-PT plus ADVANCE (which includes videotape modeling plus therapist-led discussion focused on family communication, problem solving, and coping skills) or IY-PT.[113] Although

main effects for time are reported for both mother-reported child disruptive behaviors as measured by the ECBI Problem Score [IY-PT ADVANCE baseline mean: 17.04 (7.02), IY-PT ADVANCE post-treatment mean: 10.08 (7.95), IY-PT ADVANCE short-term followup mean: 9.23 (7.10); IY-PT baseline mean: 15.55 (7.71), IY-PT post-treatment mean: 9.52 (5.94), IY-PT short-term followup mean: 6.79 (4.82)], CBCL Behavior Problems subscale [IY-PT ADVANCE baseline mean: 66.21 (8.97), IY-PT ADVANCE post-treatment mean: 58.58 (10.12), IY-PT ADVANCE short-term followup mean: 57.48 (11.05); IY-PT baseline mean: 64.09 (8.55), IY-PT post-treatment mean: 57.82 (9.60), IY-PT short-term followup mean: 55.94 (8.69)], and CBCL Social Competence subscale [IY-PT ADVANCE baseline mean: 38.48 (10.28), IY-PT ADVANCE post-treatment mean: 45.40 (14.47), IY-PT ADVANCE short-term followup mean: 45.76 (10.73); IY-PT baseline mean: 38.00 (12.58), IY-PT post-treatment mean: 43.06 (13.54), IY-PT short-term followup mean: 40.42 (10.76)] indicating significant improvement from baseline to post-treatment and short-term followup on each measure, there were no significant effects for group or the group-by-time interaction indicating no differences between groups or between groups over time. Trends for father-reported outcomes were similar to those for mother-reported outcomes for each of these measures.

Parent Management Training – Oregon Model (PMTO)

Two RCTs (1 high and 1 moderate risk of bias) examined PMTO.[117,125] One study used the CBCL[125] and the other study the ECBI[117] as its primary measure of child disruptive behaviors (Table 16).

Table 16. Summary of behavior outcomes for studies of parent-only intervention (PMTO) in school-age children

Author, Year Design (Risk of Bias) Country: N Randomized	Group	Behavior Measure	Between-Group Difference[a]
Ogden et al., 2008[125] RCT (Moderate) Norway: 112	**G1:** PMTO **G2:** Regular services	CBCL, Externalizing (T-score)	**G1 vs. G2:** p<0.05
		TRF, Externalizing (T-score)	**G1 vs. G2:** p=NS
Kjobi et al., 2012[117] RCT (High) Norway: 216	**G1:** PMTO **G2:** Regular services	ECBI, Problem	**G1 vs. G2:** p=0.01
		ECBI, Intensity	**G1 vs. G2:** p=0.002

PMTO = Parent Management Training Oregon Model; RCT = randomized controlled trial; CBCL = Child Behavior Checklist; ECBI = Eyberg Child Behavior Inventory; N = number; WLC = waitlist control; TRF = Teacher Report Form; NS = not significant

[a]The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

One RCT randomized 4 to 12 year old children (80% boys) in Norway to receive either PMTO or treatment as usual.[125] Referrals were made through the normal process at the participating children's services agencies. Children assigned to PMTO experienced statistically significant greater reductions from baseline to post-treatment (11 to 12 months post-baseline) in parent-reported child disruptive behaviors as measured by the CBCL Externalizing scale [PMTO baseline mean: 66.44 (9.09), post-treatment mean: 59.69 (9.44); treatment as usual baseline mean: 65.61 (10.75), post-treatment mean: 61.22 (9.85)], but not as measured by the Parent Daily Report (PDR). No treatment main effect was reported for teacher-reported child disruptive behaviors as measured by the TRF. No treatment main effect was reported for observed child disruptive behavior.

One RCT compared a brief version of PMTO to treatment as usual with 3 to 12 year old children (69.1% boys) whose parents contacted a primary care agency due to disruptive behaviors.[117] Results indicated that the brief version of PMTO was more effective than treatment as usual from pre- to post-treatment on parent-reported ECBI, Intensity [PMTO baseline mean: 124.94 (27.57), PMTO post-treatment mean: 106.06 (27.80); treatment-as-usual baseline mean: 124.76 (28.42); treatment-as-usual post-treatment mean: 114.43 (28.79)], ECBI, Problem [PMTO baseline mean: 15.45 (7.16), PMTO post-treatment mean: 9.79 (7.57); treatment-as-usual baseline mean: 15.02 (7.40); treatment-as-usual post-treatment mean: 11.64 (7.88)], and Merrell externalizing subscale [PMTO baseline mean: 74.17 (19.67), PMTO post-treatment mean: 64.56 (17.95); treatment as usual baseline mean: 73.72 (19.84); treatment-as-usual post-treatment mean: 68.58 (19.20)]. No significant group-by-time interactions for child disruptive behaviors as measured by teacher-reported Merrell externalizing subscale were reported.

Other Interventions With Only a Parent Component

In addition to the IY-PT and PMTO studies discussed above, six other studies examined interventions including only a parent component.[88,90,91,121,122,147] Three of these six studies measured child disruptive behaviors with the SDQ,[88,91,122] two studies used the CBCL Externalizing subscale,[90,147] one study used each of the KSADS,[121] DBRS-R,[121] Ohio Scales subscales,[90] and ECBI Intensity and Problem Scales (Table 17).[147]

Table 17. Summary of behavior outcomes for studies of parent-only intervention (other) in school-age children

Author, Year Design (Risk of Bias) Country: N Randomized	Groups	Behavior Measure	Between-Group Difference[a]
McGrath et al., 2011[121] RCT (Low) Canada: 243	**G1:** Parent Education Programme **G2:** TAU	Diagnosis	**G1 vs. G2:** p<0.001
Kling et al., 2010[122] RCT (Moderate) Sweden: 159	**G1:** PMT (practitioner assisted) **G2:** PMT (self-directed) **G3**: WLC	ECBI, Problem	**G1 vs. G2:** p<0.05 **G1 vs. G3:** p<0.001 **G2 vs. G3:** p<0.001[b]
		ECBI, Intensity	**G1 vs. G2:** p=NS **G1 vs. G3:** p<0.001 **G2 vs. G3:** p<0.001[b]
Coughlin, et al., 2009[88] NRCT (High) Ireland: 74	**G1:** Parents Plus Children's Programme **G2:** TAU	SDQ, Conduct problems	**G1 vs. G2:** p<0.01
Costin, et al., 2004[91] NRCT (High) Australia: 66	**G1:** PMT (perceptive) **G2:** PMT (skilled)	SDQ, Conduct problems	**G1 vs. G2:** p<0.01[b]
Shapiro et al., 2012[90] NRCT (High) United States: 194	**G1**: HNC **G2**: TAU	CBCL, Externalizing	**G1 vs. G2:** p=NS
Hutchings et al., 2002[147] RCT (Moderate) United Kingdom: 42	**G1**: Intensive treatment **G2:** Standard	CBCL, Externalizing (T-score)	**G1 vs. G2:** p=NS

CBCL = Child Behavior Checklist; ECBI = Eyberg Child Behavior Inventory; G = group; HNC = Helping the Noncompliant Child; N = number; NRCT = nonrandomized controlled trial; PMT = Parent Management Training; RCT = Randomized Controlled Trial; SDQ = Strengths and Difficulties Questionnaire; TAU = treatment as usual; WLC = waitlist control

[a]The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

[b] Effects favored G2.

One RCT randomized 80 children in Nova Scotia, Canada between the ages of 3 and 7 years (78% boys) with ODD to receive the Parenting the Active Child intervention or treatment as usual.[121] The primary outcome was the percentage of children no longer meeting formal criteria for a KSADS-confirmed ODD diagnosis. In comparison to treatment as usual, children with ODD randomized to receive Parenting the Active Child were significantly less likely to meet ODD diagnostic criteria at 120- and 240-days post-treatment, but were not statistically less likely to meet ODD diagnostic criteria at 365-days post-treatment (percentages by group at each time point were not given). DBRS-R scores were not reported.

One RCT compared a practitioner-directed parent management training program (PMT-P) with a self-directed parent management training program (PMT-S) and waitlist control group in a population of 3 to 10 year old children (60% boys) referred to outpatient clinics in Sweden for disruptive behaviors.[122] Active treatment was 11 weeks long. Six-month followup data are also provided. In comparison to the children in the waitlist control group, children in both PMT groups experienced statistically significantly greater reductions in parent-reported child disruptive behaviors as measured by the PDR [PMT-P baseline mean: 9.4 (3.8), PMT-P post-treatment mean: 6.0 (4.0), PMT-P 6-month followup mean: 5.0 (3.2); PMT-S baseline mean: 9.7 (3.7), PMT-S post-treatment mean: 7.6 (3.7), PMT-S 6-month followup mean: 6.4 (3.9); WLC baseline mean: 10.6 (3.9), WLC post-treatment mean: 10.1 (4.9), WLC 6-month followup data not reported], ECBI-I [PMT-P baseline mean: 137.5 (20.6), PMT-P post-treatment mean: 118.9 (25.6), PMT-P 6-month followup mean: 115.3 (25.1); PMT-S baseline mean: 137.0 (28.1), PMT-S post-treatment mean: 122.3 (30.8), PMT-S 6-month followup mean: 113.7 (29.7); WLC baseline mean: 140.2 (29.8), WLC post-treatment mean: 139.8 (28.9), WLC 6-month followup data not reported], and ECBI-P [PMT-P baseline mean: 15.5 (5.0), PMT-P post-treatment mean: 10.0 (6.9), PMT-P 6-month followup mean: 8.2 (5.9); PMT-S baseline mean: 15.2 (6.9), PMT-S post-treatment mean: 12.0 (7.5), PMT-S 6-month followup mean: 10.2 (7.1); WLC baseline mean: 16.4 (6.4), WLC post-treatment mean: 16.4 (6.5), WLC 6-month followup data not reported]. No differences were reported in child functional outcomes as measured by the parent-reported Social Competence Scale. Direct comparisons of the PMT-P and PMT-S showed significant between-group effects in favor of PMT-P for child disruptive behaviors as measured by the PDR and ECBI-P (but not the other measures) at post-treatment and that this advantage was stable over the 6-month followup period.

One study using a sequential block design to assign parents of 6 to 11 year old children (80% boys) with disruptive behaviors to the Parents Plus Children's Program (PPCP) or to treatment as usual in outpatient mental health services in Ireland.[88] Duration of active treatment was 8 weeks long. In comparison to children receiving treatment as usual, children assigned to the PPCP program experienced greater reductions in parent-reported child disruptive behaviors as measured by the SDQ total difficulties score [PPCP baseline mean: 21.19 (6.15), PPCP post-treatment mean: 18.12 (6.23); TAU baseline mean: 22.34 (7.33), TAU post-treatment mean: 22.15 (8.30)] and conduct problems score [PPCP baseline mean: 5.07 (2.06), PPCP post-treatment mean: 3.92 (1.61); TAU baseline mean: 5.28 (2.12), TAU post-treatment mean: 5.53 (2.46)].

One study assigned parents of children (83% boys) with ODD (mean age: 9.5 years) referred to a mental health clinic in metropolitan Melbourne, Australia to a Skilled Parenting group or to a Perceptive Parenting group according to parent preference.[91] Greater reductions in SDQ total difficulties were reported in the Skilled Parenting group [baseline mean: 24.18 (4.70), post-

treatment mean: 20.77 (4.77)] than in the Perceptive Parenting group [baseline mean: 24.17 (4.85), post-treatment mean: 23.44 (7.54)] over 8 weeks of active treatment.

One study sequentially assigned parents of 3 to 9 year old children (73% male) referred with disruptive behaviors to an outpatient clinic in Ohio to receive the Helping the Noncompliant Child parent intervention or to treatment as usual.[90] Although children in both groups improved on parent-reported measures of child disruptive behaviors, change from baseline to post-treatment in parent-reported child disruptive behaviors as measured by the CBCL Total Problems subscale did not differ significantly between children referred to the Helping the Noncompliant Child intervention group [baseline mean: 68.7 (8.8), post-treatment mean: 64.3 (11.1)] and treatment as usual group [baseline mean: 68.7 (8.4), post-treatment mean: 64.3 (11.3)] or on other parent-reported measures of other constructs.

One RCT randomized 2 to 10 year old children (85% boys) referred for disruptive behaviors to an outpatient clinic in the United Kingdom to receive intensive outpatient treatment or standard treatment.[147] The intensive treatment differed from the standard program primarily by its inclusion of 3 5-hour sessions that included individual units and videotaped recording of parent-child interactions in order to give feedback to parents (average service contact 25 hours in 11 visits over 24 weeks) to the standard outpatient treatment (average service contact 7 hours in 6 visits over 24 weeks). Child disruptive behavior was measured by parent-reported CBCL Externalizing subscale. Parent-reported child disruptive behaviors as measured by the CBCL mean Externalizing T-score for the standard treatment group [baseline mean: 75.3 (5.9), post-treatment: 67.0 (9.23)] and intensive group [baseline mean: 74.2 (9.28), post-treatment mean: 63.9 (11.1)] both decreased from baseline to post-treatment and statistical models showed a main effect for time but no group-by-time interaction. Importantly, only the intensive treatment group had a mean score below the clinical cut-off at post-treatment. A companion paper reporting 4-year followup reported that the intensive treatment group's mean CBCL Externalizing scores remained below the clinical cutoff and that the standard treatment group meaning CBCL scores had worsened such that improvement from baseline was no longer evident at 4-year followup.[167]

Multicomponent Interventions

Of the multicomponent intervention studies (n = 17), four studies[105,110,126,131] examined IY components delivered in combination with each other (IY-PT + IY-CT in three and IY-PT + IY-CT + IY-TT in one); two studies[128,134] assessed the Coping Power Program; two studies[97,101] examined the effects of a modular treatment for children with ODD or CD; two studies[89,137] evaluated the SNAP Under 12 Outreach Project; and seven studies[92,96,100,103,108,123,165] evaluated a different multicomponent intervention.

Incredible Years (IY)

Four studies examined IY components delivered in combination with each other (3 studies of IY-PT + IY-CT; 1 study of IY-PT + IY-CT + IY-TT) for school-age children (Table 18).[105,110,126,131]

Table 18. Summary of behavior outcomes for studies of IY interventions in school-age children

Author, Year Design (Risk of Bias) Country: N Randomized	Groups	Behavior Measure	Between-Group Difference[a]
Larsson et al., 2009[126] RCT (Moderate) Norway: 136	**G1:** IY-PT **G2:** IY-PT + IY-CT **G3:** WLC	CBCL, Aggression (father report)	**G1 vs. G2:** p=NS
		CBCL, Aggression (mother report)	**G1 vs. G3:** p<0.0167 **G2 vs. G3:** p<0.0167[b] **G1 vs. G2:** p=NS
		ECBI, Problem (father report)	**G1 vs. G2:** p<0.0167 **G1 vs. G3:** p<0.0167
		ECBI, Problem (mother report)	**G1 vs. G3:** p=NS **G2 vs. G3:** p=NS **G1 vs. G2:** p=NS
		ECBI, Intensity (father report)	**G1 vs. G3:** p<0.0167 **G2 vs. G3:** p=NS **G1 vs. G2:** p=NS
		ECBI, Intensity (mother report)	**G1 vs. G3:** p<0.0167 **G2 vs. G3:** p=NS **G1 vs. G2:** p=NS
Drugli et al., 2006[131] RCT (Moderate) Norway: 99	**G1:** IY-PT **G2:** IY-PT + IY-CT **G3:** WLC	CBCL, Aggression (teacher report)	**G2 vs. G1:** p<0.05[b] **G2 vs. G3:** p<0.01 **G1 vs. G3:** p=NS
Webster-Stratton et al., 1997[110] RCT (Moderate) United States: 97	**G1:** IY-PT **G2:** IY-CT **G3:** IY-PT + IY-CT **G4:** WLC	ECBI, Intensity (mother report)	**G1 vs. G2:** p=NS
		ECBI, Intensity (father report)	**G1 vs. G2:** p=NS
Webster-Stratton et al., 2004[105] RCT (Moderate) United States: 159	**G1:** IY-PT **G2:** IY-PT + IY-TT **G3:** IY-CT **G4:** IY-CT + IY-TT **G5:** IY-PT + IY-CT + IY-TT **G6:** WLC	ECBI, Intensity (mother report)	**G2 vs. G1**: p<0.02[c]

CBCL = Child Behavior Checklist; ECBI = Eyberg Child Behavior Inventory; G = group; N = number; NRCT = nonrandomized controlled trial; RCT = randomized controlled trial; WLC = waitlist control

[a]The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

[b]Group by time not significant; only this pairwise contrast was significant.

[c]Effects favor G2.

One RCT randomized 4 to 8 year old children (80% boys) referred to two child psychiatry outpatient clinics in Norway due to oppositional or conduct problems to IY-PT, IY-PT plus IY-CT, or to a waitlist control group.[126] Mother-reported child disruptive behaviors as measured by the ECBI Intensity scale were significantly reduced for IY-PT [baseline mean: 157.1 (24.2), post-treatment mean: 116.5 (27.0)] as compared to the waitlist control group [baseline mean: 159.7 (23.1), post-treatment mean: 137.3 (28.6)] but no significant difference between the IY-PT plus IY-CT [baseline mean: 156.5 (22.0), post-treatment mean: 121.8 (31.9)] and waitlist control group. Mother-reported aggressive behavior as measured by the CBCL Aggression subscale was significantly reduced for the IY-PT [baseline mean: 18.8 (6.8), post-treatment mean: 110 (7.0)] and IY-PT + IY-CT [baseline mean: 21.7 (7.0), post-treatment mean: 13.7 (8.6)] as compared to the waitlist control group [baseline mean: 20.0 (7.7), post-treatment mean: 17.2 (8.2)]. No significant between-group difference was reported for mother-reported ECBI-P. Generally, father-reported child disruptive behaviors correlated strongly with mother-reports.

One RCT included 4 to 8 year old children (80% boys) referred for treatment to two child psychiatric outpatient clinics in Norway by parents due to disruptive behaviors.[131] Children and their parents were randomized to receive IY-PT, IY-PT + IY-CT, or to a waitlist control condition. The PT groups lasted 12-14 weeks. The CT sessions took place over 18 weeks. Results indicate a significant main effect for group on teacher-reported aggression as measured by the Preschool Behavior Questionnaire (PBQ) for children in day care and the aggression subscale of the TRF for children in school from baseline to post-treatment, co-varying baseline scores [PT + CT baseline mean: 3.0 (1.6), PT + CT post-treatment mean: 1.8 (1.5); PT-only baseline mean: 2.7 (1.7), PT-only post-treatment mean: 2.5 (1.4); WLC baseline mean: 3.2 (1.6), WLC post-treatment mean: 3.1 (1.6)]. Teacher-reported child disruptive behavior was significantly reduced in the PT + CT group in comparison to the PT-only ($p<0.05$) and waitlist control ($p<0.01$) groups but the PT-only and waitlist control groups did not significantly differ.

One RCT randomly assigned 4 to 8 year old children (75% boys) referred to an outpatient university research clinic in the United States with conduct problems to receive IY-CT, IY-PT, combined IY-CT + IY-PT, or to a waitlist control condition.[110] Families were assessed at baseline and 8 months post-baseline (2 months after 6 months of active treatment), and 1-year post-treatment (e.g., 1.5 years post-baseline). At 1-year post-treatment followup, there were significant effects for time for all three active treatment groups on all mother and father-reports of child disruptive behaviors (CBCL Total Behavior problems score, ECBI Intensity score, and PDR score), and child social problem solving via WALLY but no significant group-by-time interactions for any of these variables. Considering all effects together, the IY-CT + IY-PT was superior to IY-CT in that it had an effect on parenting and child behaviors, and was superior to IY-PT in that it had an impact on child social problem solving.

One RCT examined the effect of IY-PT + IY-CT +IY-TT when delivered together in comparison to other combinations of IY components, to individual IY components, and to a waitlist control condition in 4 to 8 year old children (90% boys) with ODD who were referred by their families to an outpatient university research clinic in the United States.[105] Children were randomly assigned to one of the following treatment conditions: IY-PT; IY-PT + IY-TT; IY-CT; IY-CT + IY-TT; IY-PT + IY-CT + IY-TT; or a waitlist control. Although the study mainly reports results from composite measures made up of a number of previously validated measures (composite measures) because they are not themselves validated measures, are excluded from this report, it also reports the percentage of children showing clinically significant improvements at 6 months (post-treatment) and 1-year followup. At 1-year followup (e.g., the last followup), the treatment arms with the highest proportion of children showing clinically significant improvements on mother-reported ECBI-I scores were the IY-PT +IY-TT (84.6%) and IY-CT + IY-TT (81.3%) groups, but the only significant contrasts were between the IY-PT + IY-TT and IY-PT groups (with the combined treatment showing greater change) and the IY-CT group showing more improvement than the IY-PT group. It should also be noted that on teacher reported aggression via the TASB that the IY-CT group was more likely to have shown clinical improvement than the IY-PT + IY-CT + IY-TT group.

Coping Power Program

Two studies[128,134] assessed the Coping Power Program (Table 19).

Table 19. Summary of behavior outcomes for studies of Coping Power Program for school-age children

Author, Year Design (Risk of Bias) Country: N Randomized	Groups	Behavior Measure	Between-Group Difference[a]
Van de Wiel et al., 2007[128] RCT (Moderate) The Netherlands: 77	**G1:** CPP **G2:** TAU	CBCL, Externalizing	**G1 vs. G2:** p=NS
		TRF, Externalizing	**G1 vs. G2:** p=NS
Cabiya et al., 2008[134] RCT (High) Puerto Rico: 278	**G1:** CPP (culturally modified) **G2:** WLC	Bauermeister School Behavior Inventory, Irritability/Hostility	**G1 vs. G2:** p=NS

CBCL = Child Behavior Checklist; CPP = Utrecht Coping Power Program; ECBI = Eyberg Child Behavior Inventory; G = group; N = number; NRCT = nonrandomized controlled trial; NS = nonsignificant; RCT = randomized controlled trial; TAU = treatment as usual; WLC = waitlist control

[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

One RCT assigned children ages 8 to13 years referred for disruptive behaviors to one of four child psychiatric outpatient clinics or three mental health centers in the Netherlands over a 3-year period to receive either the Coping Power Program (CPP) or treatment as usual.[128,168] Significant group-by-time interactions were reported only for PDR overt aggression subscale [CPP baseline mean: 2.90 (1.51), CPP post-treatment mean: 1.90 (1.38); treatment as usual baseline mean: 2.46 (1.53); treatment as usual post-treatment mean: 2.05 (1.43)], but not for the other parent-reported measures of child disruptive behavior (e.g., PDR oppositional behavior subscale, CBCL Externalizing Behavior subscale) or for the teacher-reported measure of child disruptive behavior via the TRF externalizing behavior subscale. At 5-year followup, there were no significant differences between the CPP or TAU groups on the NYS Delinquency Scale [CPP mean: 1.2 (1.5); TAU mean: 1.5 (1.5)], but children in the CPP group did report being less likely than children in the TAU group to smoke cigarettes in the past month (CPP % smoked in the last month = 17; TAU % smoked in the last month = 42) and lifetime use of marijuana (CPP % with lifetime marijuana use = 13; TAU % with lifetime marijuana use = 35).[168]

A second RCT randomly assigned 278 children from 8 to 13 years of age in Puerto Rico who met *DSM-IV-TR* criteria for a disruptive behavior disorder to receive a culturally sensitive cognitive behavioral intervention (n = 174) or to a waitlist control group (n = 104).[134] Behavioral outcomes were measured with the Irritability / Hostility subscale of the Bauermeister School Behavior Inventory. Although boys and girls in the treatment group demonstrated more improvement on this subscale score over 12 weeks of than did children in the control group, these differences were not statistically significantly different.

Modular

Two studies[97,101] (each including multiple papers) examined the effects of a modular treatment for children with ODD or CD (Table 20). The modular treatment included seven components: (1) child CBT/skills training, (2) child medication for ADHD, (3) parent management training, (4) parent-child / family therapy, (5) school programming/teacher consultation, (6) peer relations/community activities development, and (7) case/crisis management.

Table 20. Summary of behavior outcomes for studies of modular intervention in school-age children

Author, Year Design (Risk of Bias) Country: N Randomized	Groups	Behavior Measure	Between-Group Difference[a]
Kolko et al., 2009[101] RCT (Moderate) United States: 139	**G1:** Modular treatment (community) **G2:** Modular treatment (clinic)	CBCL, Externalizing	**G1 vs. G2:** p=NS
		CBCL (teacher report)	**G1 vs. G2:** p=NS
Kolko et al., 2010[97] RCT (Moderate) United States: 163	**G1:** Modular treatment **G2:** EUC	SDQ, Total Score (parent report)	**G1 vs. G2:** p=NS
		SDQ, Total Score (teacher report)	**G1 vs. G2:** p=NS
		Individualized Goal Achievement Rating	**G1 vs. G2:** p<0.0.5

CBCL = Child Behavior Checklist; ECBI = Eyberg Child Behavior Inventory; EUC = enhanced usual care; G = group; N = number; NRCT = nonrandomized controlled trial; NS = nonsignificant; RCT = randomized controlled trial; SDQ = Strengths and Difficulties Questionnaire; WLC = waitlist control

[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

One RCT included children aged 6 to11 years (85% boys) referred for disruptive behavior disorders to program sites associated with a university medical center in the United States.[101] Children and families were randomly assigned to receive the modular treatment either in the community or in an outpatient research clinic setting. Healthy controls were included to provide norms for self-report questionnaires. Results suggest significant improvement in both groups from baseline to post-treatment (6 months) on measures of child disruptive behaviors including the CBCL Externalizing subscale, IOWA Conners Rating Scale oppositional defiant subscale, Self-Report of Antisocial Behavior (SRAB), TRF externalizing behavior, and Child and Adolescent Functional Assessment Scale (CAFAS). There were not group-by-time interactions from baseline to post-treatment or at 3-year followup for any measures indicating that the modular treatment can be successfully implemented in a research clinic or community based setting.

One RCT examines the effectiveness of the same modular treatment adapted for implementation by nurses in primary care settings.[97] To examine this, children aged 6 to 11 years (65% boys) were enrolled based on parent concerns about disruptive behaviors and scores on the Pediatric Symptoms Checklist (or PSC-17) above the clinical cutoff for externalizing behavior problems to either the nurse-administered modular care (PONI) or to enhanced usual care (EUC). From baseline to 1-year followup, significant group-by-time interactions were seen on the Individualized Goal Achievement Rating (IGAR) average [PONI baseline mean: 1.0 (0.0), post-treatment mean: 2.8 (0.8); EUC baseline mean: 1.0 (0.0), EUC post-treatment mean: 2.6 (0.8)] and Child Health and Illness Profile (CHIP) total score [PONI baseline mean: 47.3 (5.9), PONI post-treatment mean: 49.5 (5.9); EUC baseline mean: 48.7 (6.0), EUC post-treatment mean: 48.9 (6.1)], but not on the parent-reported PSC-17 externalizing score, parent-reported SDQ total score, or teacher-reported SDQ total score even though both groups reported change over time for almost all of these measures.

SNAP Under 12 Outreach Project (SNAP Under 12 ORP)

Two studies evaluated the SNAP Under 12 in Canada (Table 21).[89,137]

Table 21. Summary of behavior outcomes for studies of the SNAP Under 12 ORP intervention in school-age children

Author, Year Design (Risk of Bias) Country: N Randomized	Groups	Behavior Measure	Between-Group Difference[a]
Augimeri et al., 2007[137] RCT (Moderate) Canada: 32	**G1:** SNAP ORP **G2:** Control	CBCL, Aggression	**G1 vs. G2:** p=0.006
		CBCL, Delinquency	**G1 vs. G2:** p=0.007
Lipman et al., 2008[89] NRCT (High) Canada: 339	**G1:** SNAP ORP **G2:** WLC	CBCL, Aggression	**G1 vs. G2:** p=0.01
		TRF, Aggression	**G1 vs. G2:** p=NS

CBCL = Child Behavior Checklist; ECBI = Eyberg Child Behavior Inventory; G = group; N = number; NRCT = nonrandomized controlled trial; RCT = randomized controlled trial; SNAP ORP = SNAP Under 12 Outreach Project; WLC = waitlist control
[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

One RCT included children (mean age approximately 9 years; approximately 75% boys) who had police contact within 6 months of referral and/or a T-score on the CBCL Delinquency subscale indicating behavior problems more serious than 98 percent of same-age and same-sex peers.[137] Children were randomized to receive the SNAP Under 12 12-week outpatient program or to a waitlist control group that participated in a recreation group called the Cool Runner's Club. From baseline to 3 months, children in the SNAP Under 12 group experienced significantly greater declines in parent-reported child disruptive behaviors as measured by the CBCL Delinquency [baseline mean: 8.9, 3-month mean: 4.9, SDs not given] and aggression [baseline mean: 18.8, 3-month mean: 15.5, SDs not given] subscale mean scores than did children referred to the waitlist control group [delinquency subscale baseline mean: 8.9, delinquency subscale 3-month mean: 8.4; aggression subscale baseline mean: 19.4, aggression subscale 3-month mean: 19.0, SDs not given]. At the 3-month point, the two groups switched treatments and from 3 months to 18 months, the children originally referred to SNAP Under 12 continued to make progress and the children originally referred to the waitlist control (who were now receiving SNAP Under 12) also showed improvement (although they never caught up to the other group) on the same measures.[137]

In a second study, investigators recruited boys ages 6 to 11 years from the community to participate in SNAP Under 12 using similar inclusion and exclusion criteria as described in the previous study but allocated children to SNAP Under 12 or the waitlist control recreation group on a first-come, first-served basis rather than being randomized.[89] In comparison to children initially referred to the waitlist control condition, children initially referred to the SNAP Under 12 showed significantly more improvement on parent-reported child disruptive behaviors as measured by the CBCL Rulebreaking, Aggressive, Conduct Problems, and Total Problems subscales, but not on the CBCL Competence subscale or TRF outcomes.

Other Multicomponent Interventions

Seven studies, each evaluating a different multicomponent intervention, were also identified (Table 22).[92,96,100,103,108,123,165]

Table 22. Summary of behavior outcomes for studies of other interventions in school-age children

Author, Year Design (Risk of Bias) Country: N Randomized	Groups	Behavior Measure	Between-Group Difference[a]
Boylan, et al., 2013[96] RCT (Moderate) United States: 166	**G1:** MF-PEP **G2:** TAU	ODD symptoms	**G1 vs. G2:** p=NS
Scott et al., 2010[123] RCT (Low) United Kingdom: 112	**G1:** SPOKES **G2:** TAU	ECBI, Intensity	**G1 vs. G2:** p<0.016
		ODD symptoms (teacher reported)	**G1 vs. G2:** p=NS
Jouriles et al., 2009[100] RCT (High) United States: 66	**G1:** Project Support **G2:** No clinical services	CBCL, Externalizing	**G1 vs. G2:** p<0.05
		ECBI, Intensity[b]	**G1 vs. G2:** p<0.05[c]
Greene et al., 2004[103] RCT (Moderate) United States: 50	**G1:** CPS **G2:** Parent Training	ODDRS	**G1 vs. G2:** p=NS
Kolko et al., 2001[108] RCT (Moderate) United States: 54	**G1:** CBT **G2:** Education **G3:** Home visit	Fire-setting behavior, Child	**G1 vs. G2:** p<0.06 **G1 vs. G3:** p<0.06
Masi et al., 2014[92] NRCT (Moderate) Italy: 135	**G1:** MTP **G2:** TAU	CBCL, Externalizing	**G1 vs. G2:** p=NS
		CBCL, Aggression	**G1 vs. G2:** p<0.01[d]
Barrett et al., 2000[165] RCT (High) Australia: 57	**G1:** RST **G2:** WLC	CBCL, Externalizing (mother report)	**G1 vs. G2:** p<0.05

CBCL = Child Behavior Checklist; CPS = Collaborative Problem Solving; ECBI = Eyberg Child Behavior Inventory; G = group; MTP = multimodal treatment program; N = number; NRCT = nonrandomized controlled trial; ODD = Oppositional Defiant Disorder Rating Scale; RCT = randomized controlled trial; RST = reciprocal skills training; SPOKES = Supporting Parents on Kids Education in Schools; TAU = treatment as usual; WLC = waitlist control

[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

[b] Publication reports as ECBI Problem, but scores indicate ECBI Intensity.

[c] Difference was significant at followup but not significant at end of treatment.

[d] As reported in the publication, authors report p values using the "greater than" symbol (e.g., p>X.X). For purposes of this report, we assume that this was an error and that the where the publication references statistical significance and nonsignificance, the intention was to use the "less than" symbol. Effect favors G1 unless noted otherwise.

One RCT evaluated the effectiveness of a CBT as compared to an educational fire safety intervention or a home visit from a firefighter for fire-setting behavior in 54 boys aged 5 to 13 years and referred due to documented fire-setting behavior by the City of Pittsburgh Bureau of Fire, direct parental solicitation, or a mental health practitioner.[108] Children in each of the three intervention groups showed significant improvement on measures of fire involvement, interest and risk, but CBT and fire safety intervention were not more effective at reducing fire-setting behaviors even though the group-by-time interaction approached statistical significance ($p<0.06$).[108]

One RCT assigned children between the ages of 4 and12 years (68% boys) clinically referred to an outpatient mental health clinic specializing in the treatment of disruptive behavior disorders at a university teaching hospital and meeting criteria for ODD to receive Collaborative Problem Solving (CPS) or parent training based on Barkley's (1997) 10-week behavior management program.[103] The primary measure of child disruptive behavior was the parent-rated Oppositional Defiant Disorder Rating Scale (ODDRS). On this measure of parent-reported child disruptive behaviors, there was a significant change from baseline to post-treatment and from baseline to 4-

month followup for children in the CPS group, but the group-by-time interactions from baseline to post-treatment and from baseline to 4-month followup were not significant (means for both groups at each time point are not given). The group-by-time interactions on the Parent-Child Relationship Inventory (PCRI), a measure of one of this reviews functional outcomes, was also not significant.

One RCT assigned children between 8 and11 years (73% boys) with mood disorders and their families to receive either treatment as usual plus immediate treatment in the multifamily psycho-education program (MF-PEP) or treatment as usual plus waitlist control.[96] Disruptive behaviors were measured with the Children's Interview of Psychiatric Syndromes (ChIPS) and Parent Form (P-ChIPS). Although MF-PEP was associated with a significant decrease in ODD symptoms from baseline to 12 months followup, there was no significant difference between the MF-PEP [baseline mean: 5.7 (2.1), 12-month followup: 4.5 (2.6)] and the waitlist control groups [baseline mean: 5.4 (2.6), 12-month followup: 4.9 (2.7)] on ODD symptoms. There was also no difference in CD symptoms from baseline to 12-month followup.

One RCT assigned parents of children with a mean just over 5 years of age (71% boys) who were screened for disruptive behaviors with the SDQ in schools in London to either receive the Supporting Parents on Kids Education in Schools (SPOKES) intervention or to receive access to a telephone hotline designed to help parents access treatment as usual in the community over 28 weeks of active treatment.[123] In comparison to children in the control group, children receiving SPOKES had significant reductions in child antisocial behavior as measured by parent interview [SPOKES baseline mean: 1.15 (0.44), SPOKES post-treatment mean: 0.91 (0.36); treatment as usual baseline mean: 1.12 (0.49), treatment as usual post-treatment mean: 1.13 (0.49)], parent-reported child disruptive behavior as measured by the ECBI Intensity subscale) [SPOKES baseline mean: 119.1 (31.6), SPOKES post-treatment mean: 103.9 (27.3); treatment as usual baseline mean: 115.9 (27.0), treatment as usual post-treatment mean: 113.2 (31.3)], but little difference in teacher-reported oppositional symptoms as measured by a *DSM-IV* questionnaire items.

An additional RCT examining Project Support and was conducted in the United States. Authors examined the effectiveness of Project Support, a family intervention specifically designed to reduce disruptive behaviors in the children of women at a domestic violence shelter.[100] The intervention provides mothers with child behavior management skills and instrumental and emotional support.[100] Although therapists worked primarily alone with mothers, children were regularly included in sessions so that mothers' skill using the new techniques could be evaluated and additional skill building activities could be tailored according to the child's response to them. Child conduct problems were measured by two maternal self-report measures (CBCL Externalizing and ECBI Intensity). Mean CBCL Externalizing scale scores decreased from 67.9 to 57.4 pre- to post-treatment for the Project Support group and from 65.9 to 61.6 for the treatment as usual control group (Cohen's d=0.66) and from 142.1 to 102.5 and 129.8 to 102.7 on the ECBI Intensity scale (Cohen's d=0.17), respectively.

One moderate risk of bias, prospective cohort study[92] compared children sequentially assigned to a multimodal treatment program (MTP), which includes once a week sessions for 1 year of individual and group support for children and individual parent training, or treatment as usual (TAU). The study sample consisted of 135 youth with a mean age of 12.0 (2.5) years. Mean CBCL Externalizing scores decreased in the MTP group from 69.73 (7.43) at baseline to 65.58 (7.34) at end of treatment and from 71.49 (7.25) at baseline to 68.58 (7.62) at end of treatment in the treatment as usual group. Mean CBCL Aggressive Behavior scores decreased in

the MTP group from 71.67 (9.03) at baseline to 66.81 (8.52) at end of treatment and from 74.06 (9.77) at baseline to 71.17 (10.00) at end of treatment in the TAU group. The mean CBCL Delinquent Behavior scores decreased in the MTP group from 66.03 (8.07) at baseline to 63.42 (7.51) at end of treatment and in the TAU group from 67.90 (8.31) at baseline to 65.20 (7.92) at end of treatment. This group-by-time interaction was not statistically significant.

Finally, one high risk of bias RCT[165] compared children assigned to a reciprocal skills training (RST), a family-based treatment, against children assigned to a waitlist control group. The study sample consisted of 57 children with a mean age of 8.47 (1.6) years. The intervention group consisted of children referred from a clinic setting and from a pre-treatment hospital setting. Because studies of inpatient hospital settings are excluded from this review, only results for the clinic setting are reported here. On the parent-reported CBCL Externalizing scale, mean scores for the clinic-referred RST group decreased from 67.4 (7.0) at baseline to 59.8 (11.5) end of treatment and from 70.0 (5.8) to 74.0 (5.0) for the waitlist control group. The group-by-time interaction effect was statistically significant. In addition, the percentage of children who no longer met *DSM-IV* criteria for oppositional defiant disorder was significantly reduced in the clinic-referred RST group than in the waitlist control group (72.2% vs. 30%, p<0.01).

Summary of Key Disruptive Behavior Outcomes

We report the behavior outcomes measured by CBCL (Table 23) or ECBI (Table 24) from studies of school-age children.

Table 23. Outcome summary for change in disruptive behavior symptoms reported by CBCL in studies of school-age children

Author, Year, Design (Risk of Bias)	Group (Participants Analyzed)	Scale	Baseline Mean (SD)	Last Followup Mean (SD)	Between-Group Difference[a]
van Manen et al., 2004[132] RCT (Moderate)	**G1:** Social cognitive (42) **G2:** Social skills training (40) **G3:** WLC (NA)	CBCL, Externalizing	**G1:** 66.8 (9.5) **G2:** 69.7 (6.6) **G3:** 68.3 (5.9)	12 months post-intervention **G1:** 58.8 (10.8) **G2:** 59.4 (10.7) **G3:** NA	**G1 vs. G2:** p=NS
		TRF	**G1:** 71.6 (6.7) **G2:** 71.4 (10.1) **G3:** 69.0 (9.0)	12 months post-intervention **G1:** 64.9 (7.4) **G2:** 63.1 (10.4) **G3:** NA	**G1 vs. G2:** p=NS
Larsson et al., 2009[126] RCT (Moderate)	**G1:** IY-PT (40) **G2:** IY-PT + IY-CT (48) **G3:** WLC (NA)	CBCL, Aggression (father report)	**G1:** 14.8 (5.0) **G2:** 19.8 (8.4) **G3:** 17.4 (8.2)	12 months post-intervention **G1:** 8.6 (4.3) **G2:** 12.1 (8.4) **G3:** NA	**G1 vs. G2:** p=NS
		CBCL, Aggression (mother report)	**G1:** 18.8 (6.8) **G2:** 21.7 (7.0) **G3:** 20.0 (7.7)	12 months post-intervention **G1:** 11 (7.0) **G2:** 12.7 (7.4) **G3:** NA	**G1 vs. G3:** p<0.0167 **G2 vs. G3:** p<0.0167 **G1 vs. G2:** p=NS

Table 23. Outcome summary for change in disruptive behavior symptoms reported by CBCL in studies of school-age children (continued)

Author, Year, Design (Risk of Bias)	Group (Participants Analyzed)	Scale	Baseline Mean (SD)	Last Followup Mean (SD)	Between-Group Difference[a]
van de Wiel et al., 2007[128] RCT (Moderate)	**G1:** CPP (38) **G2a:** Family Therapy (10) **G2b:** Behavior therapy (16)	CBCL, Externalizing	**G1:** 74.6 (6.4) **G2a:** 77.1 (6.4) **G2b:** 73.3 (8.9)	**End of treatment** G1: 69.6 (8.4) G2a: 72.6 (7.9) G2b: 67.8 (9.8)	G1 vs. G2: p=NS Mean improvement: G1 vs. G2a: 0.07; G1 vs. G2b: −0.07
		TRF, Externalizing	**G1:** 64.9 (9.9) **G2a:** 66.4 (7.9) **G2b:** 65.8 (11.0)	End of treatment **G1:** 62.4 (10.7) **G2:** 66.7 (9.5) **G3:** 60.6 (12.6)	**G1 vs. G2:** p=NS Mean improvement: **G1 vs.** G2a: 0.37; **G1 vs.** G2b: −0.29
Webster-Stratton et al., 1997[110] RCT (Moderate)	**G1:** IY-PT (26) **G2**: IY-CT (24) **G3**: IY-PT + IY-CT (22) **G4**: WLC (NR)	CBCL, Total Problems (T-score, mother report)	**G1:** 65.5 (7.8) **G2:** 67.1 (7.9) **G3:** 65.3 (6.1) **G4:** 67.9 (7.7)	12 months post-intervention **G1:** 55.1 (10.6) **G2:** 58.6 (10.7) **G3:** 57.7 (8.7) **G4:** NR	**G1 vs. G2:** p<0.001
		CBCL, Total Problems (T-score, father report)	**G1:** 62.7 (7.9) **G2:** 64.3 (8.3) **G3:** 66.2 (7.8) **G4:** 62.0 (8.6)	12 months post-intervention **G1:** 53.5 (8.9) **G2:** 54.8 (13.1) **G3:** 57 (11.3) **G4:** NR	**G1 vs. G2:** p<0.01
Augimeri et al., 2007[137] RCT (Moderate)	**G1:** SNAP ORP(16) **G2:** Control (14)	CBCL, Delinquency	**G1:** 8.9 (NR) **G2:** 8.9 (NR)	18 months **G1:** 3.1 (NR) **G2:** 6.5 (NR)	**G1 vs. G2:** p=0.007
		CBCL, Aggression	**G1:** 18.8 (NR) **G2:** 19.4 (NR)	18 months **G1:** 11.0 (NR) **G2:** 18.1 (NR)	**G1 vs. G2:** p=0.006
Hutchings et al., 2002[147] RCT (Moderate)	**G1:** PT, intensive (21) **G2:** Standard treatment (13)	CBCL, Externalizing	**G1:** 74.2 (9.3) **G2:** 75.3 (5.9)	6 months post-intervention **G1:** 63.9 (11.1) **G2:** 67 (9.2)	**G1 vs. G2:** p=NS

Table 23. Outcome summary for change in disruptive behavior symptoms reported by CBCL in studies of school-age children (continued)

Author, Year, Design (Risk of Bias)	Group (Participants Analyzed)	Scale	Baseline Mean (SD)	Last Followup Mean (SD)	Between-Group Difference[a]
Lipman et al., 2008[89] NRCT (High)	**G1:** SNAP ORP (132) **G2:** WLC (77)	CBCL, Aggression	**G1:** 80.3 (10.6) **G2:** 78.1 (9.6)	6 months post-intervention **G1:** 72 (11.1) **G2:** 73.4 (10.7)	**G1 vs. G2:** p=0.01
		CBCL, Rulebreaking	**G1:** 73.2 (6.6) **G2:** 70.9 (6.9)	6 months post-intervention **G1:** 67.5 (8.2) **G2:** 67.6 (7.2)	**G1 vs. G2:** p=0.02
		CBCL, Conduct Problems	**G1:** 77.6 (8) **G2:** 75.8 (7.4)	6 months post-intervention **G1:** 70.7 (9.6) **G2:** 72 (7.5)	**G1 vs. G2:** p=0.01
	G1: SNAP ORP (102) **G2:** WLC (67)	TRF, Aggression	**G1:** 67.1 (11.0) **G2:** 69.1 (10.4)	6 months post-intervention **G1:** 66.3 (11.0) **G2:** 67.7 (12.3)	**G1 vs. G2:** p=NS
		TRF, Rulebreaking	**G1:** 64.2 (8.5) **G2:** 66.1 (8.4)	6 months post-intervention **G1:** 63.5 (8.2) **G2:** 64.0 (9.2)	**G1 vs. G2:** p=NS
		TRF, Conduct Problems	**G1:** 66.7 (11.3) **G2:** 70.2 (12.0)	6 months post-intervention **G1:** 65.1 (10.5) **G2:** 67.7 (12.8)	**G1 vs. G2:** p=NS
Kolko et al., 2009[101] RCT (Moderate)	**G1:** Modular treatment (community) (69) **G2:** Modular treatment (clinic) (70)	CBCL, Externalizing	**G1:** 29.9 (8.8) **G2:** 28.9 (9.5)	36 months post-intervention **G1:** NR **G2:** NR	**G1 vs. G2:** p=NS
	G1: Modular treatment (community) (63) **G2:** Modular treatment (clinic) (66)	TRF	**G1:** 30.1 (16.2) **G2:** 30.7 (15.8)	36 months post-intervention **G1:** NR **G2:** NR	**G1 vs. G2:** p=NS
Ogden et al., 2008[125] RCT (Moderate)	**G1:** PMTO (52) **G2:** Regular services (45)	CBCL, Externalizing (T-score)	**G1:** 66.4 (9.1) **G2:** 59.9 (9.9)	12 months post-intervention **G1:** 59.7 (9.4) **G2:** 90 (9.8)	**G1 vs. G2:** p<0.05
	G1: PMTO (52) **G2:** Regular services (45)	TRF, Externalizing (T-score)	**G1:** 63.9 (9.8) **G2:** 58.4 (9.2)	12 months post-intervention **G1:** 60.7 (10.7) **G2:** 57.2 (8.6)	**G1 vs. G2:** p=NS
Shapiro et al., 2012[90] NRCT (High)	**G1:** HNC (Manualized) (70) **G2:** TAU (124)	CBCL, Externalizing	**G1:** 71.5 (9.4) **G2:** 71.3 (9.9)	End of treatment **G1:** 67.7 (11.2) **G2:** 66.9 (11.2)	**G1 vs. G2:** p=NS

Table 23. Outcome summary for change in disruptive behavior symptoms reported by CBCL in studies of school-age children (continued)

Author, Year, Design (Risk of Bias)	Group (Participants Analyzed)	Scale	Baseline Mean (SD)	Last Followup Mean (SD)	Between-Group Difference[a]
Jouriles et al., 2009[100] RCT (High)	**G1:** Project support (32) **G2:** No clinical services (34)	CBCL, Externalizing	**G1:** 67.9 (NR) **G2:** 65.9 (NR)	20 months post-intervention **G1:** 53.3 (NR) **G2:** 59.0 (NR)	0.63 (95% CI: 0.04 to 1.20)[b]
Webster-Stratton et al., 1994[113] RCT (Moderate)	**G1:** IY-PT (ADVANCE) (38) **G2:** IY-PT (basic) (39)	CBCL, Total Problem (mother report)	**G1:** 66.21 (8.97) **G2:** 64.09 (8.55)	**G1:** 57.48 (11.05) **G2:** 55.94 (8.69)	**G1 vs. G2:** p=NS
		CBCL, Total Problem (father report)	**G1:** 64.41 (7.89) **G2:** 61.54 (9.45)	13 weeks post-intervention **G1:** 56.57 (55.45) **G2:** 55.46 (8.66)	**G1 vs. G2:** p=NS
Masi et al., 2014[92] NRCT (Moderate)	**G1**: MTP (64) **G2**: TAU (71)	CBCL, Externalizing	**G1**: 69.73(7.43) **G2**: 71.49 (7.25)	24 months post-intervention **G1:** 63.57 (9.34) **G2:** 68.52 (9.10)	**G1 vs. G2:** p=NS
Barrett et al., 2000[165] RCT (High)	**G1**: RST (23) **G2**: WLC (12)	CBCL, Externalizing (mother report)	**G1**: 67.4 (7.0) **G2**: 70.0 (5.8)	End of intervention **G1**: 59.8 (11.5) **G2**: 74.0 (5.0)	**G1 vs. G2:** p<0.05

CBCL = Child Behavior Checklist; CPP = Utrecht Coping Power Program; HNC = Helping the Noncompliant Child; IY = Incredible Years; PT = parent training; CT = child training; NA = not applicable; NRCT = nonrandomized controlled trial; NR = not reported; PCOH = prospective cohort study; PMTO = Parent Management Training-Oregon; SNAP ORP = Stop Now and Plan Under 12 Outreach Project; RCT = randomized controlled trial; TRF = Teacher Report Form; WLC = waitlist control

[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

[b] Cohen's d (confidence interval) for difference in means between post-intervention and last followup.

Table 24. Outcome summary for change in disruptive behavior symptoms reported by ECBI in studies of school-age children

Author, Year Design (Risk of Bias)	Group (Participants Analyzed)	Scale	Baseline Mean (SD)	Last Followup Mean (SD)	Between-Group Difference[a]
Larsson et al., 2009[126] RCT (High)	**G1:** PT (40) **G2:** PT + CT (48) **G3:** WLC (NA)	ECBI, Problem (father report)	**G1:** 16.6 (6.4) **G2:** 15.6 (6.3) **G3:** 15.1 (8.4)	12 month post-intervention **G1:** 7.0 (5.5) **G2:** 8.3 (7.5) **G3:** NA	NR
		ECBI, Problem (mother report)	**G1:** 20.7 (6.2) **G2:** 20.2 (6.3) **G3:** 19.8 (4.8)	12 months post-intervention **G1:** 11.1 (8.4) **G2:** 10.2 (8.1) **G3:** NA	NR
		ECBI, Intensity (father report)	**G1:** 140.3 (21.2) **G2:** 143.8 (23.2) **G3:** 142.9 (29.7)	12 months post-intervention **G1:** 108.9 (22.3) **G2:** 116.1 (24.3) **G3:** NA	NR
		ECBI, Intensity (mother report)	**G1:** 157.1 (24.2) **G2:** 156.5 (22) **G3:** 159.7 (23.1)	12 months post-intervention **G1:** 121.3 (28.8) **G2:** 119.1 (31.4) **G3:** 137.3 (28.6)	NR
Jouriles et al., 2009[100] RCT (High)	**G1:** Project support (32) **G2:** No clinical services (34)	ECBI, Intensity	**G1:** 142.1 (NR) **G2:** 129.8 (NR)	20 months post-intervention **G1:** 82.8 (NR) **G2:** 103.8 (NR)	0.66 (95% CI: 0.03 to 1.26)[b]
Kjobi et al., 2012[117] RCT (High)	**G1:** PMTO (108) **G2:** Regular services (108)	ECBI, Problem	**G1:** 15.5 (7.2) **G2:** 15.0 (7.4)	2 weeks post-intervention **G1:** 9.8 (7.6) **G2:** 11.6 (7.9)	**G1 vs. G2:** p=0.01
		ECBI, Intensity	**G1:** 124.9 (27.6) **G2:** 124.8 (28.4)	2 weeks post-intervention **G1:** 106.1 (27.8) **G2:** 114.4 (28.8)	**G1 vs. G2:** p=0.002
Axberg et al., 2012[118] RCT (High)	**G1:** IYP (34) **G2:** WLC (20)	ECBI, Problem	**G1:** 20.8 (4.2) **G2:** 20.4 (6.6)	12 months post-intervention **G1:** 11.1 (7.9) **G2:** 17.5 (8.0)	**G1 vs. G2:** p=0.003
		ECBI, Intensity	**G1:** 160 (20.3) **G2:** 152.9 (23.6)	12 months post-intervention **G1:** 128.6 (26.5) **G2:** 147.1 (26.0)	**G1 vs. G2:** p=0.001
Kling et al., 2010[122] RCT (High)	**G1:** PMT-P (58) **G2:** PMT-S (61) **G3:** WLC (NA)	ECBI, Problem	**G1:** 15.5 (5) **G2:** 15.2 (6.9) **G3:** 16.4 (6.4)	6 months post-intervention **G1:** 8.2 (5.9) **G2:** 10.2 (7.1) **G3:** NA	**G1 vs. G2:** p<0.05
		ECBI, Intensity	**G1:** 137.5 (20.6) **G2:** 137 (28.1) **G3:** 140.2 (29.8)	6 months post-intervention **G1:** 115.3 (25.1) **G2:** 113.7 (29.7) **G3:** NA	**G1 vs. G2:** p=NS

Table 24. Outcome summary for change in disruptive behavior symptoms reported by ECBI in studies of school-age children (continued)

Author, Year Design (Risk of Bias)	Group (Participants Analyzed)	Scale	Baseline Mean (SD)	Last Followup Mean (SD)	Between-Group Difference[a]
Gardner et al., 2006[130] RCT (High)	G1: IY-PT (38) G2: WLC (NA)	ECBI, Problem	G1: 20.8 (6.5) G2: 20.3 (7)	**18 months post baseline G1: 12.9 (9.3) G2: NA**	**G1 vs. G2[c]:** p=0.05
		ECBI, Intensity	**G1**: 152.7 (39.2) **G2**: 156.1 (32.9)	18 months post baseline **G1**: 134 (41) **G2**: NA	**G1 vs. G2[c]**: p=0.01
Brestan et al., 1997[114] RCT (Moderate)	**G1**: PCIT **G2**: WLC	ECBI, Problem	**G1**: 23 (5.8) **G2**: 24 (5.4)	End of intervention **G1**: 11 (10.7) **G2**: 24 (7.5)	**G1 vs. G2:** p=0.0001
		ECBI, Intensity	**G1**: 173 (29.5) **G2**: 176 (30.2)	End of intervention **G1**: 133 (37.7) **G2**: 170 (36)	**G1 vs. G2:** p=0.0001

CT=Child Training; ECBI=Eyberg Child Behavior Inventory; EOT=end of treatment; IY-PT=Incredible Years Program – Parent Training; NA=Not Applicable; NR=Not Reported; PT=Parent Training; PMTO=Parent Management Training Oregon Model; PMT-P=Parent Management Training- Perceptive; PMT-S=Parent Management Training- Skilled; RCT=Randomized controlled trial; WLC=waitlist control

[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

[b] Cohen's d (confidence interval) for difference in means between post-intervention and last followup.

[c] 6 months post-intervention.

Teenage Children

Description of Included Studies

We identified 14 studies,[86,94,104,106,111,115,116,120,124,136,142-144,146] reported in 17 papers[86,94,104,106,111,115,116,120,124,136,142-144,146,169-171] that evaluated psychosocial interventions for teenagers with disruptive behaviors. Of the 14 included studies, 13 were RCTs (4 high, 5 moderate, and 4 low risk of bias)[94,104,106,111,115,116,120,124,136,142-144,146]and one was a retrospective cohort study (high risk of bias).[86] Six of the studies were conducted in the United States;[94,104,106,111,115,116] three were conducted in Germany;[142-144] two were conducted in the Netherlands;[86,136] and one each in the United Kingdom,[120] Israel,[146] and Sweden.[124] One study included only a child component.[104] The other 13 studies were multicomponent interventions (Table 25). Of these multicomponent interventions, six were family interventions[106,115,116,142-144] and five were Multisystemic Therapy (MST).[94,111,120,124,136] We categorized the other two multicomponent intervention studies as an "other" multicomponent intervention.

Table 25. Summary of interventions and risk of bias for studies of psychosocial interventions in teenage children with DBD

Intervention		High Risk of Bias	Moderate Risk of Bias	Low Risk of Bias	All
Single Component					1
	Child only	1	-	-	1
Multicomponent					13
	Family therapy	1	2	2	6
	MST	1	1	2	5
	Other	1	-	-	2
Total		**5**	**5**	**4**	**14**

MST = Multisystemic Therapy

Detailed Analysis

Interventions With Only a Child Component

One single center, RCT (high risk of bias) conducted in the United States examined an intervention with a child component only.[104] This study examined the efficacy of the Adolescents Coping with Depression (CWD-A) course in a population of non-incarcerated adolescents between 13 and 17 years meeting *DSM-IV* criteria for comorbid conduct disorder and depression (n = 93). These results were compared to a control condition utilizing a group intervention focused on life skills and tutoring (LS) only. The CWD-A is a group-based cognitive behavioral intervention typically directed towards depressive symptoms. However, his study also examined its impact on disruptive behavior. Participants were randomized to receive either the CWD-A course (n = 45) or the control LS intervention (n = 48). Approximately 10 adolescents per group (CWD-A group mean: 10.4 participants; LS mean: 9.4 participants) were treated in sixteen 2-hour sessions over the course of 8 weeks. They were then assessed post-treatment and at 6- and 12-month followup using the following dimensional outcome measures: the Beck Depression Inventory-II (BDI-II), the Hamilton Depression Rating Scale (HDRS), the Externalizing Problem Subscale of the Child Behavior Checklist (CBCL), the Children's Global Assessment Scale (CGAS), and the Social Adjustment Scale-Self Report (SAS-R). Mean (SD) age of participants was 15.1 (1.5) years for those in the CWD-A group and 15.1 (1.3) years in the LS control group and 55 percent in the sample were male. Comparing baseline demographic and clinical characteristics, the two randomized groups only differed significantly in gender, the CWD-A group consisting of 60 percent females compared to only 38 percent females in the LS condition. Thus, gender was included as a covariate during analysis.

From baseline to the end of active treatment at 12 months, the children randomized to the CWD-A intervention group showed significant improvement compared to the LS control group in the depressive outcome measures (BDI-II, HDRS, SAS-R). However, no significant reductions were reported in disruptive behaviors as measured by the parent-reported CBCL Externalizing subscale, or in social functioning, as measured by the CGAS.

Multicomponent Interventions

Of the 13 studies of multicomponent interventions for teenage children, six studies examined family interventions including the Brief Strategic Family Therapy (n = 3),[106,142,144] Parenting with Limits and Love,[116] a family behavior therapy intervention,[115] and a general family therapy approach (n = 1).[143] Five of the multicomponent intervention studies evaluated Multisystemic

Therapy (MST).[94,111,120,124,136] The two other studies each examined a different multicomponent intervention.[86,146]

Family Therapy

Six studies examined the impact of family therapy interventions on disruptive behaviors and other related outcomes (Table 26).[106,142-144] Three of these studies were conducted in Germany[142-144] and three were conducted in the United States.[106,115,116] Two of the studies measured disruptive behaviors using the self-reported Adolescent Risk Taking Behavior Scale (ARBS),[142,143] while another study used the conduct disorder and socialized aggression subscales of the parent-reported Revised Behavior Problem Checklist (RBPC) behavior problem scale.[106] Three studies also measured levels of anger and anger expression using the self-report State-Trait Anger Expression Inventory (STAXI)[142-144] Three studies also included outcomes related to health related quality of life,[142-144] two included interpersonal functioning outcomes[142,143] and one measured the impact of the intervention on family functioning.[106]

Table 26. Summary of studies of multicomponent interventions (family therapy) for teenage children

Author, Year Design (Risk of Bias) Country: N Randomized	Group	Behavior Measure	Between-Group Difference[a]
Santisteban et al., 2003[106] RCT (High) United States: 126	**G1:** BSFT **G2:** Group therapy	RBPC, Conduct problem	**G1 vs. G2:** p<0.01
		RBPC, Socialized aggression	**G1 vs. G2:** p<0.01
Nickel et al., 2006[142] RCT (Low) Germany: 40	**G1:** BSFT **G2:** Placebo Intervention Program	STAXI, State-Anger	**G1 vs. G2:** p<0.001
		ARBS, Drug use	**G1 vs. G2:** p<0.001
Nickel et al., 2006[144] RCT (Moderate) Germany: 72	**G1:** BSFT **G2:** Placebo Intervention Program	STAXI, State-Anger	**G1 vs. G2:** p<0.01
Nickel et al., 2005[143] RCT (Low) Germany: 44	**G1:** Family therapy **G2:** Placebo Intervention Program	STAXI, State-Anger	**G1 vs. G2:** p<0.001
		ARBS, Drug use	**G1 vs. G2:** p<0.001 (EOT) **G1 vs. G2:** p=0.29 (Last FU)
Azrin et al., 2001[115] RCT (High) United States: 56	**G1**: FBT **G2**: ICPS	CBCL, Delinquency	**G1 vs. G2:** p<0.001
		YSR, Delinquency	**G1 vs. G2:** p<0.001
		ECBI, Problem	**G1 vs. G2:** p<0.001
		ECBI, Intensity	**G1 vs. G2:** p<0.001
		Court House records: Frequency of arrests	**G1 vs. G2:** p<0.001
Sells et al., 2011[116] RCT (Moderate) United States: 38	**G1**: PLL **G2**: TAU	CBCL, Externalizing	**G1 vs. G2:** p<0.01
		CBCL, Aggressive Behaviors	**G1 vs. G2:** p<0.01
		CBCL, Rule-Breaking Problems	**G1 vs. G2:** p<0.01

EOT = end of treatment; FU = followup; FBT = Family Behavioral Therapy; ICPS = Individual Cognitive Problem Solving; RCT = randomized controlled trial; BSFT = Brief Strategic Family Therapy; PLL = Parenting with Love and Limits; STAXI = State-Trait Anger Expression Inventory; ARBS = Adolescents Risk-taking Behavior Scale

[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

Three of the four studies examined the delivery of BSFT and its impact on disruptive behavior problems and related outcomes.[106,142,144] In each of these studies the intervention group receiving BSFT was compared to a control group intervention in which the participants received

either group therapy[106] or another family-based intervention.[142,144] Each of these studies examined the use of BSFT with a specific population. One study[106] compared the effectiveness of BSFT for a primarily male Hispanic adolescent population (n = 126, mean age: 15.6 years; 75% male) with a general group therapy based intervention. Participants were included based on parental or school complaints of externalizing behavior problems. Compared to the control group, participants receiving the BSFT intervention displayed a significantly greater reduction in behavior problems as measured by the Revised Behavior Problem Checklist (RBPC). Compared to 11 percent of clinically significant improvement in the control group (p=NS), 43 percent of the BSFT group showed reliable improvement in Conduct Disorder measures (p<0.001). Similarly, on the Socialized Aggression scale, 36 percent of BSFT recipients showed reliable improvement (p<0.001) compared to 11 percent of the control population (ns). The treatment group also reported significant reductions in substance use and increased improvements in family functioning as compared to the control group.

Two studies evaluated the impact of BSFT on bullying behaviors: one[142] in a population of adolescent females and the other[144] with adolescent males. The first study compared the effectiveness of BSFT on bullying behavior in a group of 15 year old girls [n = 40, mean age: 15.5 (0.5) years] who had shown direct verbal and/or physical bullying behavior for at least six months to a placebo intervention. The study assessed risk-taking behaviors using the Adolescent Risk Taking Behavior Scale (ARBS), which consisted of seven behavior scales: drug use, smoking, binge drinking, excessive media use, having sex without a condom, having sex while using drugs and alcohol and sexual disinhibition. The study found that girls receiving the BSFT showed significantly greater reductions in adolescent risk taking behavior than those receiving the placebo treatment at both the end of treatment (ARBS score mean difference between groups: −9.3, p<0.001) and after a one year followup assessment (ARBS score mean difference between groups: −8.2, p<0.001). BSFT also led to significant improvements in interpersonal relationships as measured by the Inventory of Interpersonal Problems (IIP-D), as well as reducing levels of anger (STAXI) and increasing health related quality of life (SF-36) as compared to the placebo intervention. These results were reported to have remained relatively stable at one-year followup.

One study[143] examined the effectiveness of family therapy as a monotherapy for reducing disruptive behaviors and anger compared to a placebo intervention. This study utilized an integrative family therapy model that integrated elements from family systems theory, psychodynamic-oriented therapy, gestalt therapy, and behavioral therapy. Interventions were focused around communication, family rules and each family member's role in the existing problematic family system presentation. Forty-four male adolescents [mean age: 15.2 (0.5)] displaying bullying behavior participated in the study, half randomly assigned (n = 22) to receive a family therapy program for 6 months and the other half assigned (n = 22) to the placebo control group for the same length of time Consistent with the results from the female [mean age: 15.5 (0.5)] cohort study,[142] this study reported significantly greater reductions in adolescent risky behaviors on all scales of the ARBS (end-of-treatment ARBS score mean difference: −6.3, p<0.001; followup ARBS score mean difference: −3.1, p<0.001) and significant reductions in anger levels on nearly all of the scales measured by the STAXI. Additional reported outcomes included significant improvements in interpersonal relationships, as measured by six of the eight scales on the IIP-D, and significant improvement in health related quality of life (SF-36) as compared to the placebo control group.

One high risk of bias RCT[115] compared children assigned to family-behavioral therapy with children assigned to individual cognitive therapy. The study sample consisted of 56 children with

a mean age 15.4 (1.3) years. On the parent-reported CBCL Delinquency scale children assigned to the family-behavioural therapy group experienced greater reductions [baseline mean score: 74.44 (6.70); end of treatment mean score: 63.55 (9.10)] than did children assigned to the individual cognitive therapy group [baseline mean score: 77.40 (8.45); end of treatment mean score: 66.67 (12.11)]. These differences were maintained at 6-month followup. Similar findings were also evident via the parent reported ECBI Problem scale (family behavioural therapy group baseline mean score: 17.86 (8.52); family behavioural therapy group end of treatment mean score: 8.58 (9.09); individual cognitive therapy group baseline mean score: 21.52 (6.12), individual cognitive therapy group end of treatment mean score: 11.95 (9.46)], and ECBI Intensity scale (family behavioural therapy group baseline mean score: 133.55 (38.26); family behavioural therapy group end of treatment mean score: 90.78 (36.37); individual cognitive therapy group baseline mean score: 145.93 (35.58); individual cognitive therapy group end of treatment mean score: 110.35(45.92)].

One moderate risk of bias RCT[116] compared Parenting with Limits and Love (PLL), a 6-week group therapy program integrating principles of a structural family therapy approach, against a control group receiving TAU probation services including counseling, community schools, and/or community service. The study sample included 38 teenagers [mean age: 15] (57% boys) who had been referred for criminal offenses. Disruptive behaviors were assessed via the parent-reported CBCL. Mean scores in the intervention group showed greater decrease than in the control group on the CBCL Externalizing subscale (intervention group baseline mean score: 64.07 (15.80), intervention group end of treatment mean score: 56.57 (11.21); control group baseline mean score: 73.08 (9.54), control group end of treatment mean score: 71.83 (10.11)], aggressive behaviors scale (intervention group baseline mean score: 67.43 (12.77), intervention group end of treatment mean score: 58.14 (6.78); control group baseline mean score: 70.83 (14.22), control group end of treatment mean score: 71.67 (13.01)], and rule-breaking behaviors scale (intervention group baseline mean score: 67.29 (10.94), intervention group end of treatment mean score: 60.07 (8.07); control group baseline mean score: 75.33 (7.30), control group end of treatment mean score: 69.33 (9.44)]. The group-by-time interaction for each of these measures was statistically significant.

Multisystemic Therapy

Of the five studies that examined MST, two were conducted in the United States,[94,111] and one each in the Netherlands,[136] the United Kingdom,[120] and Sweden.[124] All five of these studies were RCTs (1 high, 2 moderate, and 2 low risk of bias). Overall, the treatment effects were positive, with only one study[124] not demonstrating significance (Table 27).

Table 27. Summary of studies of multicomponent interventions (MST) for teenage children

Author, Year Design (Risk of Bias) Country: N Randomized	Group	Behavior Measure	Between-Group Difference[a]
Weiss et al., 2013[94] RCT (Moderate) United States: 164	**G1:** MST **G2:** TAU	CBCL, Externalizing	**G1 vs. G2:** p<0.05
		YSR, Externalizing	**G1 vs. G2:** p<0.05
		TRF, Externalizing	**G1 vs. G2:** p=NS
		SRD, Delinquency	**G1 vs. G2:** p=NS
		SRD, Drug Use	**G1 vs. G2:** p=NS
Borduin et al., 1995[111] RCT (Moderate) United States: 176	**G1:** MST **G2:** IT	Symptom Checklist, 90-item (self-report)	**G1 vs. G2:** p=NS
		RBPC, z-score (mother report)	**G1 vs. G2:** p<0.05

Table 27. Summary of studies of multicomponent interventions (MST) for teenage children (continued)

Author, Year Design (Risk of Bias) Country: N Randomized	Group	Behavior Measure	Between-Group Difference[a]
Butler et al., (2011)[120] RCT (Low) United Kingdom: 108	**G1:** MST **G2:** Usual Services	CBCL, Aggression	**G1 vs. G2:** p<0.05
		CBCL, Delinquency	**G1 vs. G2:** p<0.05
		CBCL, Externalizing	**G1 vs. G2:** p=NS
		YSR, Externalizing	**G1 vs. G2:** p=NS
		YSR, Aggression	**G1 vs. G2:** p=NS
		YSR, Delinquency	**G1 vs. G2:** p=NS
Sundell et al., (2008)[124] RCT (Low) Sweden: 139	**G1:** MST **G2:** TAU	CBCL, Externalizing	**G1 vs. G2:** p=NS
		YSR, Externalizing	**G1 vs. G2:** p=NS
Asscher et al., 2013[136] See: Asscher et al., 2014[171] RCT (High) Netherlands: 256	**G1:** MST **G2:** TAU	CBCL, Externalizing	**G1 vs. G2:** p<0.05
		YSR, Externalizing	**G1 vs. G2:** p<0.05
Asscher et al., 2014[171] Related to: Asscher et al., 2013[136]	**G1**: MST **G2**: TAU	CBCL, Externalizing	**G1 vs. G2:** p<0.001
		DBD rating, ODD Subscale	**G1 vs. G2:** p<0.001
		DBD rating, CD subscale	**G1 vs. G2:** p<0.001
		YSR, Externalizing	**G1 vs. G2:** p<0.01
		SRD, Violent offenses	**G1 vs. G2:** p=NS
		SRD, Property offenses	**G1 vs. G2**: p<0.01

RCT = randomized controlled trial; MST = Multisystemic Therapy; IT = individual therapy; NS = nonsignificant; RBPC = Revised Behavior Problem Checklist; SRD = Self-Reported Delinquency Scale; TAU = treatment as usual; TRF = Teacher Report Form; YSR = Youth Self-Report

[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

One study[94,172] conducted in the United States randomly assigned 164 adolescents (83% male) between the ages of 11 and 18 years in one school system's self-contained behavior intervention classrooms to receive MST or treatment as usual. Treatment as usual included behavior management interventions and support provided as part of the classroom structure. At 18-month followup, parent-reported CBCL Externalizing mean scores for the MST group [baseline mean: 25.90 (10.63); end of active treatment mean: 18.20 (10.82); change: 30% reduction] decreased significantly more from baseline to end-of-treatment than those of the control group [baseline mean: 23.40 (9.61); end of active treatment mean: 19.19 (10.36); change: 18% reduction]. The outcomes from the YSR assessment showed similar results, with the MST group [baseline mean: 17.63 (9.03); end of active treatment mean: 13.87 (8.53); change: 21% reduction] showing greater effects than the control group [baseline mean: 17.00 (7.97); end of active treatment mean: 14.22 (7.72); change: 16% reduction]. No significant effect was found based on the TRF of externalizing behaviors or arrest data.

One pretest-posttest control group design (moderate risk of bias)[111] conducted in the United States compared the effects of MST to individual therapy (IT) on criminal behavior and violent offenses among a group of high-risk juvenile offenders (n = 176, 67% male). Ninety-two participants [mean age: 14.8 (1.5)] were randomly assigned to receive MST, with 77 completing both pre- and post-treatment assessments and receiving an average of 23.9 (8.2) hours of treatment. Out of the 84 participants initially assigned to the IT control group, 63 completed both assessments and received an average of 28.6 (9.8) hours of treatment.

This study demonstrated MST to be significantly more effective than individual therapy based on several outcome measures. From pre-treatment to post-treatment, both mothers and fathers from the MST group showed significant decreases in psychiatric symptomology as measured by the SCL-90-R [mother mean baseline score: 0.12 (1.02); mother mean post-treatment score: −0.15 (0.97); father mean baseline score: −0.06 (0.90); father mean post-treatment score: −0.07 (0.77)]. Their IT counterparts did not show similar reductions in psychiatric symptomatology for either of the parents [mother mean baseline score: 0.04 (1.17); mother mean post-treatment score: 0.20 (1.26); father mean baseline score: 0.06 (1.05); father mean post-treatment score: 0.19 (1.09)]. The study also showed a significant interaction effect for mothers' reports of adolescent disruptive behaviors as measured by the Revised Behavior Problem Checklist (RBPC), with mothers in the MST group reporting a decrease in adolescent behavior problems and mothers of youths in the IT group reporting an increase in behavior problems. Additionally, adolescents in the MST group showed significant positive change in family functioning and cohesion (FACES-II), lower re-arrest rates, and less serious offenses when rearrested. The pattern of lower frequency and decreased seriousness of crimes emerged in both the analysis of the entire sample as well as when analyzing only those that completed treatment.

Three studies[120,124,136] examined the effectiveness of MST to treatment as usual in more socialized systems offering comprehensive management of disruptive behavior problems (i.e., United Kingdom, Sweden, and The Netherlands). One low risk of bias study[120] conducted in the United Kingdom compared MST to outcomes for youth working with a Youth Offending Team (YOT). YOTs, like MST, provide a multicomponent intervention that is led by a social worker working with additional team members, such as therapists and probation officers. This study examined the impact of MST versus YOT, or usual services, on offending behavior based on police records (primary outcomes), as well as parent and youth rated reports of disruptive and delinquent behaviors as measured by the CBCL and YSR (secondary outcomes). A group of 108 adolescents between 13 and 17 years of age were allocated to receive either MST [n = 56; mean age: 182.7 (12.3) months; 91% male] or YOT [n = 52; mean age: 180.6 (12.9) months; 90% male]. Based on data derived from police computer records, youth who participated in MST had significantly less nonviolent offending by the end of the followup period (18 months post treatment end). There were no significant differences with regard to violent offending given the low number of youth with violent offense records.

In regards to secondary outcome measures, assessments from baseline to 6 months post-treatment indicated that, for internalizing and externalizing problems, there was no significant difference in disruptive behaviors between the two groups. However, the CBCL scales pertinent to the hypothesis each showed significant interactions favoring MST. For the aggression subscale, MST participants showed significantly more improvement [baseline mean: 69.4 (12.9); 6-month mean: 64.2 (11.4); change: 7.5% reduction] than the YOT group [baseline mean: 66.9 (11.6); 6-month mean: 65.9 (11.9); change: 1.5% reduction]. Similar results occurred with the delinquency subscale, with MST participants again showing significant reductions in [baseline mean: 73.4 (8.3); 6-month mean: 67.9 (8.6); change: 7.5% reduction] compared to the YOT group [baseline mean: 73.0 (7.9); 6-month mean: 70.9 (8.5); change: 2.9% reduction]. Analysis of rates of change also indicated moderate effect sizes in the MST group (aggression effect size: 0.42; delinquency effect size: 0.64) and smaller effect sizes for the YOT group (aggression effect size: 0.09; delinquency effect size: 0.25). While the parent-reported outcomes suggested improvement in disruptive behaviors in the MST group, none of the scales from the YSR yielded

significant interactions. Data regarding longer-term follow up of rate of disruptive behavior were not available.

One multicenter low risk of bias study[124] examined the effectiveness of MST to treatment as usual in Sweden. Treatment as usual for court-referred youth in Sweden includes referral for social service supports, which work to identify treatment needs. Treatment in the control group was varied and was primarily represented by individual therapy, family therapy, mentoring, or no services. A group of youths between the ages of 12 and 17 fulfilling diagnostic criteria for conduct disorder [n = 156; mean age: 15.0 (1.4) years; 61% male] were randomized to either the treatment (n = 79) or control group (n = 77). Mean enrollment in MST lasted 145.8 (51.6) days. Disruptive and delinquent behavior was assessed by both caregiver and adolescent ratings through the CBCL and YSR, respectively. Additionally, the study looked at delinquency through the Self-Report Delinquency Scale (SRD), substance use measures through multiple self-reporting methods (i.e. AUDIT/DUDIT), and relationships and social competence (i.e. Pittsburgh Youth Study, SCPQ, Social Skills Rating System, school attendance). Pre- to posttest measurements did not demonstrate any significant differences in the MST intervention compared to treatment as usual as measured by the CBCL and YSR measures, nor on the SOC scale. Both groups showed decreased disruptive and delinquent behavior, improvement in social skills and better family relations.

One RCT (high risk of bias)[136] examined the effectiveness of MST compared to treatment as usual in The Netherlands. In The Netherlands, treatment as usual relies more frequently on in-home services, but also includes individual treatment, some combination of both or no services. The study included 256 adolescents [mean age: 16.02 (1.31) years; 73% male] randomly allocated to either MST or treatment as usual interventions. Researchers used the CBCL Aggression and Delinquency subscales to assess externalizing behaviors and delinquency. Parents also filled out several symptom scales from the Disruptive Behaviors Disorder rating scales. Adolescents self-reported using YSR and SRD assessments. According to both parent and youth self-reports, MST was significantly more effective at reducing externalizing behavior problems [CBCL baseline mean: 23.32 (12.60); CBCL end-of-treatment mean: 17.64 (11.57); change: 24% reduction] than treatment as usual [CBCL baseline mean: 22.55 (12.95); CBCL end-of-treatment mean: 19.25 (10.56); change: 15% reduction]. The YSR showed similar results, with a 16 percent reduction in the MST group and only a 3 percent reduction in the treatment as usual group. MST was also more effective at decreasing ODD and CD, as compared to treatment as usual. With regard to self-report of delinquent behaviors, MST demonstrated significant reductions for property offenses, but no significant effect was found for violent offending. Interestingly, further analysis of other secondary outcomes- such as parent and adolescent cognitions, parenting behavior and peer relationships- and demographic variables yielded unexpected results. While MST was equally effective across ages and ethnicity, the intervention showed larger effects for adolescent cognitions for boys than for girls. At 6-month post-treatment follow-up, there was evidence of sustained effects of MST in comparison to TAU with maintenance of statistically significant reductions in externalizing problems, ODD, and CD, but the number of re-arrests and time to re-arrest did not differ between the groups.[171]

Other Multicomponent Interventions

One RCT (moderate risk of bias)[146] examined the effect of a semi-structured bibliotherapy intervention aimed to decrease aggressive behavior in youth (Table 28). The study was conducted in the Druze community in Israel, which is a closed society living in generally segregated cities or villages. Seventy-five children (77% male) were randomly and equally

assigned to one of three conditions: child treatment only, mother plus child treatment and no treatment at all. The additional parent group was aimed at increasing parent's understanding of their child's aggressive behavior. Researchers measured aggression using a reduced version of the aggression and delinquency subscales of the CBCL questionnaire as reported by parents (CBCL), the adolescents (YSR), and their teachers (TRF). Another parent report, Coping with Children's Negative Emotions Scale (CCNS), was also used. Both treatment groups, the child group and the parent/child combination group, were more effective at reducing aggressive behavior than no treatment at all. However, the combined intervention was not significantly more effective at reducing disruptive behaviors than the child training only intervention. While obtained means demonstrated a greater decrease in aggressive behavior of the combined treatment intervention, significance was only found with the self-report measure, not with the parent or teacher report. Thus, the researchers' hypothesis of enhanced outcomes with the additional parent component was only partially supported.

Table 28. Summary of studies of multicomponent interventions (other) for teenage children

Author, Year Design (Risk of Bias) Country: N Randomized	Group	Behavior Measure	Between-Group Difference[a]
Shechtman and Birani-Nasaraladin, 2006[146] RCT (Moderate) Israel: 75	**G1:** Child only treatment **G2:** Mother plus child **G3:** Control	Modified CBCL, Aggression (YSR)	**G1 vs. G3:** p<0.001 **G2 vs. G3:** p<0.001
		Modified CBCL, Aggression (TRF)	**G1 vs. G3:** p<0.001 **G2 vs. G3:** p<0.001
		Modified CBCL, Aggression (Parent)	**G1 vs. G3:** p<0.001 **G2 vs. G3:** p<0.001
van der Put et al., 2013[86] NRCT (High) Netherlands: 192	**G1**: FFT **G2**: CBT **G3**: CBT + PT	Official conviction records: Recidivism	**G1 vs. G2:** p=NS

NRCT = nonrandomized controlled trial; N = number; FFT = Functional Family Therapy; CBT = Cognitive-Behavioral Therapy; PT = parent training; CBCL = Child Behavior Checklist; TRF = Teacher Report Form; YSR = Youth Self Report; G = group; NS = nonsignificant

[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

A nonrandomized cohort study (high risk of bias)[86] conducted in The Netherlands did not report positive treatment effect for disruptive behavior problems (Table 28). The study compared the effectiveness of treatments being offered in a forensic youth outpatient clinic at reducing recidivism. Treatments included functional family therapy (FFT) (n = 55), individual CBT (n = 87), and CBT combined with parent training (n = 50). In addition to these treatments, some youths also participated in Aggression Replacement Training (ART) (n = 27). It should be noted that both FFT and ART were implemented as trial versions and most implementing therapists had not been formally trained in administering these interventions. The official records of the 192 adolescents completing treatment in the outpatient clinic (mean age: 17.0 years; 85% male) were analyzed retrospectively, with occurrences of recidivism serving as the primary outcome measure. The study found no significant differences in 2-year total or violent recidivism rates between the different treatment interventions. However, researchers did find a higher recidivism rate for those youth who had additionally participated in ART (54% recidivism compared to 30% for non-ART juveniles), even after controlling for the type of offense committed (i.e. violent). There was also no significance found in recidivism between the treatment groups as compared to youth who dropped out of treatment (n = 42). The study found a significant interaction between

moderating variables regarding patient characteristics (ethnicity), intensity and frequency of treatment, and the therapist conducting the training.

Summary of Key Disruptive Behavior Outcomes

We report the behavior outcomes measured by CBCL, YRF, or TRF (Table 29) from studies of teenage children.

Table 29. Summary of disruptive behavior outcomes reported by ASEBA[a] in teenage children

Author, Year Study Design (Risk of Bias)	Group (Participants Analyzed)	Scale	Baseline Mean (SD)	Last Followup Mean (SD)	Between-Group Difference[b]
Rohde et al., 2004[104] RCT (High)	**G1:** CBT (41)[c] **G2:** Control (life skills) (46)[c]	CBCL, Externalizing	**G1:** 27 (15.3) **G2:** 30.9 (12.8)	12 months post-intervention **G1:** 20.8 (15.8) **G2:** 14 (9.6)	**G1 vs. G2:** p=NS
Weiss et al., 2013[94] RCT (Moderate)	**G1:** MST (84) **G2:** Treatment as usual (80)	CBCL, Externalizing	**G1:** 25.9 (10.6) **G2:** 23.4 (9.6)	18 months **G1:** 18.2 (10.8) **G2:** 19.2 (10.4)	**G1 vs. G2:** p<0.05
		Achenbach (TRF)	**G1:** 22.9 (12.5) **G2:** 22.5 (11.7)	18 months **G1:** 19.5 (12.4) **G2:** 20.1 (12.6)	**G1 vs. G2:** p=NS
		Achenbach (YSR)	**G1:** 17.6 (9.0) **G2:** 17.0 (8.0)	18 months **G1:** 13.9 (8.5) **G2:** 14.2 (7.7)	**G1 vs. G2:** p<0.05
Sundell et al., 2008[124] RCT (Low)	**G1:** MST (79) **G2:** Treatment as usual (77)	CBCL, Externalizing	**G1:** 81.8 (17.6) **G2:** 77.9 (17.4)	7 months post-intervention **G1:** 72.1 (17.1) **G2:** 69.9 (19.1)	**G1 vs. G2:** p=NS
		Achenbach (YSR)	**G1:** 69.4 (14.6) **G2:** 71 (15.9)	7 months post-intervention **G1:** 65.2 (15.6) **G2:** 64.9 (15.1)	**G1 vs. G2:** p=NS
Asscher et al., 2013[136] RCT (High)	**G1:** MST (147) **G2:** Treatment as usual (109)	CBCL, Externalizing	**G1:** 23.3 (12.6) **G2:** 22.6 (13.0)	6 months post randomization **G1:** 17.6 (11.6) **G2:** 19.3 (10.6)	**G1 vs. G2:** p<0.05
		Achenbach (YSR)	**G1:** 12.4 (9.3) **G2:** 12.4 (8.3)	6 months post randomization **G1:** 10.4 (7.9) **G2:** 12.0 (7.6)	**G1 vs. G2:** p<0.05

Table 29. Summary of disruptive behavior outcomes reported by ASEBA[a] in teenage children (continued)

Author, Year Study Design (Risk of Bias)	Group (Participants Analyzed)	Scale	Baseline Mean (SD)	Last Followup Mean (SD)	Between-Group Difference[b]
Butler et al., 2011[120] RCT (Low)	**G1:** MST (53) **G2:** Youth offending teams (51)	Achenbach Externalizing (YSR)	**G1:** 53.8 (10.7) **G2:** 54.6 (10.2)	6 months post randomization **G1:** 52.8 (11) **G2:** 51 (10.8)	**G1 vs. G2:** p=NS
		Achenbach Aggression (YSR)	**G1:** 59.1 (10.4) **G2:** 59.2 (8.1)	6 months post randomization **G1:** 57.3 (10.4) **G2:** 56.6 (8)	**G1 vs. G2:** p=NS
		Achenbach Delinquency (YSR)	**G1:** 65.1 (8.8) **G2:** 65.6 (8.1)	6 months post randomization **G1:** 62.9 (9.8) **G2:** 63.3 (9.9)	**G1 vs. G2:** p=NS
		CBCL, Externalizing	**G1:** 67.7 (8.4) **G2:** 66.4 (9.8)	6 months post randomization **G1:** 63.4 (10.2) **G2:** 63.7 (9.9)	**G1 vs. G2:** p=NS
		CBCL, Delinquency	**G1:** 73.4 (8.3) **G2:** 73 (7.9)	6 months post randomization **G1:** 67.9 (8.6) **G2:** 70.9 (8.5)	**G1 vs. G2:** p<0.05
		CBCL, Aggression	**G1:** 69.4 (12.9) **G2:** 66.9 (11.6)	6 months post randomization **G1:** 64.2 (11.4) **G2:** 65.9 (11.9)	**G1 vs. G2:** p<0.05
Shechtman and Birani-Nasaraladin. 2006[146] RCT (Moderate)	**G1:** Child only treatment (25) **G2:** Mother plus child (25) **G3:** Control (25)	Modified CBCL, Aggression (YSR)	**G1:** 9.7 (NR) **G2:** 10.6 (NR) **G3:** 12.7 (NR)	3 months **G1:** 5.1 (NR) **G2:** 3.97 (NR) **G3:** 10.7 (NR)	**G1<G2[d]** **G1>G3** **G2>G3**
		Modified CBCL, Aggression (TRF)	**G1:** 13.8 (NR) **G2:** 11.2 (NR) **G3:** 11.4 (NR)	**G1:** 5.04 (NR) **G2:** 2.88 (NR) **G3:** 9.44 (NR)	**G1=G2[d]** **G1>G3** **G2>G3**
		Modified CBCL, Aggression (Parent)	**G1:** 7.2 (NR) **G2:** 8.1 (NR) **G3:** 8.9 (NR)	3 months **G1:** 4.0 (NR) **G2:** 3.3 (NR) **G3:** 9.3 (NR)	**G1=G2[d]** **G1>G3** **G2>G3**
Azrin et al., 2001[115] RCT (High)	**G1**: FBT (29) **G2**: ICPS (27)	CBCL, Delinquency	**G1**: 74.44 (6.70) **G2**: 77.40 (8.45)	6 months post-intervention **G1**: 65.83 (10.25) **G2**: 64.15 (8.32)	**G1 vs. G2:** p<0.001
		YSR, Delinquency	**G1**: 68.55 (11.0) **G2**: 69.03(10.31)	6 months post-intervention **G1**: 60.67 (6.52) **G2**: 60.19 (9.0)	**G1 vs. G2:** p<0.001
		Courthouse records: Frequency of arrests	**G1**: 0.93 (1.51) **G2**: 0.84 (1.02)	6 months post-intervention **G1**: 0.51 (0.59) **G2**: 0.24 (0.29)	**G1 vs. G2:** p<0.001

Table 29. Summary of disruptive behavior outcomes reported by ASEBA[a] in teenage children (continued)

Author, Year Study Design (Risk of Bias)	Group (Participants Analyzed)	Scale	Baseline Mean (SD)	Last Followup Mean (SD)	Between-Group Difference[b]
Sells et al., 2011[116] RCT (Moderate)	**G1**: PLL (19) **G2**: TAU (19)	CBCL, Externalizing	**G1**: 64.07 (15.80) **G2**: 73.08 (9.54)	12 months post-intervention **G1**: 56.57 (11.21) **G2**: 71.83 (10.11)	**G1 vs. G2:** p<0.01
		CBCL, Aggressive Behaviors	**G1**: 67.43 (12.77) **G2**: 70.83 (14.22)	12 months post-intervention **G1**: 58.14 (6.78) **G2**: 71.67 (13.01)	**G1 vs. G2:** p<0.01
		CBCL, Rule-Breaking Problems	**G1**: 67.29 (10.94) **G2**: 75.33 (7.30)	12 months post-intervention **G1**: 60.07 (8.07) **G2**: 69.33 (9.44)	**G1 vs. G2:** p<0.01

CBCL = Child Behavior Checklist; CBT = Cognitive-Behavioral Therapy; FBT = Family Behavioral Therapy; ICPS = Individual Cognitive Problem Solving; MST = Multisystemic Therapy; NR = not reported; PLL = Parenting with Love and Limits; RCT = randomized controlled trial; TRF = Teacher Report Form; YSR = Youth Self-Report

[a]The CBCL is part of the Achenbach System of Empirically Based Assessment (ASEBA). There are two other components of the ASEBA - the Teacher's Report Form (TRF) is to be completed by teachers and the Youth Self-Report (YSR) by the child or adolescent.

[b]The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

[c]Number at last followup.

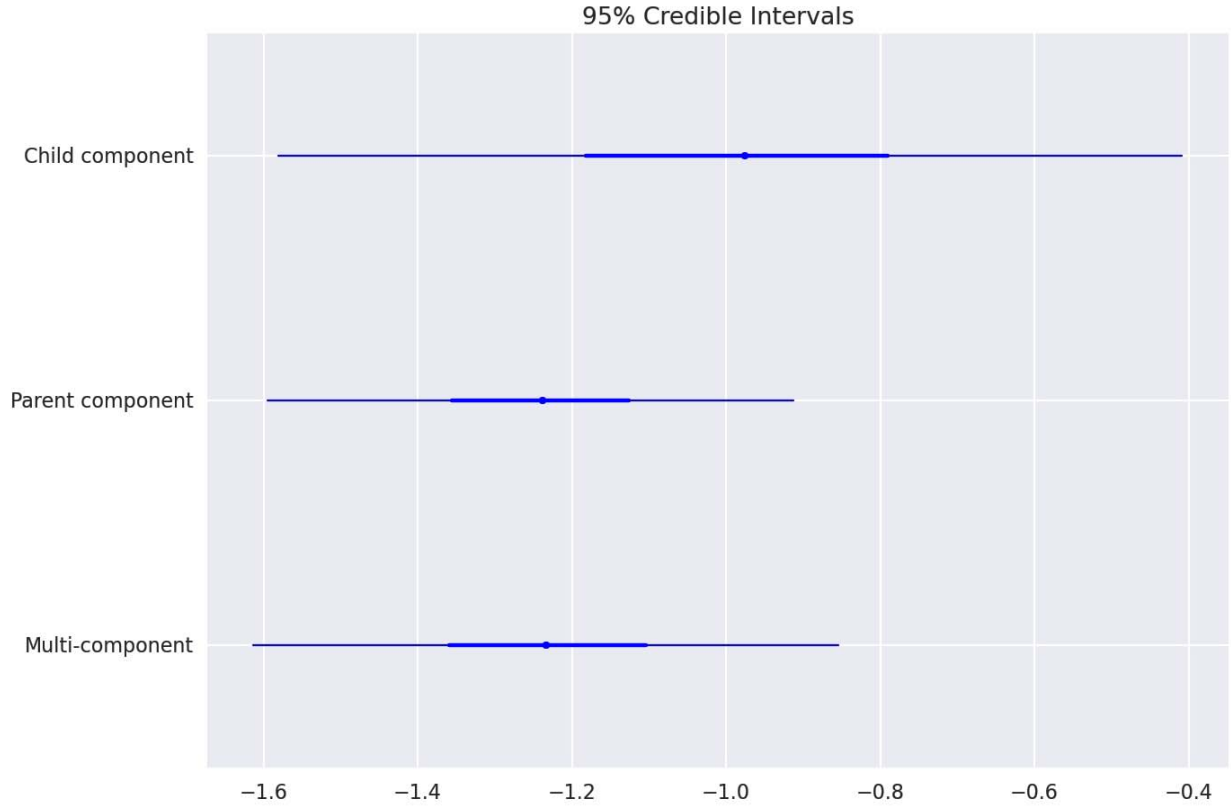
[d] post hoc analysis, p value not reported. F-score significant (p<0.001) for condition by time interaction for all three groups.

Bayesian Meta-Analysis of Psychosocial Interventions

Convergence diagnostics showed no evidence for lack of convergence in the 50,000 samples used for inference. Model fit was assessed using posterior predictive checks,[173] which revealed no strong evidence of lack of fit.

To aid interpretation, the effect sizes estimated by our model can be interpreted as the expected change in score for the intervention category relative to treatment as usual or control, in standard deviation units (negative values are reductions in score). Thus, a value of −1 is an expected reduction in score of one standard deviation under the associated treatment. The effect size for the multicomponent interventions and interventions with only a parent component had the same estimated value (Figure 3), with a median of −1.2 standard deviations reduction in outcome score (95% credible intervals: −1.6 to −0.9). The estimate for interventions with only a child component was −1.0 (95% credible interval: −1.6 to −0.4).

Figure 3. Effect size estimates



Both the multicomponent intervention category and the interventions with only a parent component had the highest posterior probability (43%) of being the best intervention (defined as having the largest effect size), followed by interventions with only a child component (14%).

Age effects were relatively more subtle, with an additive median effect of −0.4 standard deviations (95% credible interval: −0.6 to −0.3) for preschool relative to school-age children (baseline level), and of −0.1 standard deviations (95% credible interval: −0.5 to 0.2) for adolescents relative to school-age children. These trends were evident across each of the outcome measures included in the analysis.

A summary of estimated overall treatment outcomes is shown in Figures 4-6 for each treatment class, as well as for control/treatment as usual. Results are presented separately for each included outcome measure and age group.

Figure 4. Summary of estimated overall treatment outcomes (ECBI Intensity Subscale) in studies of preschool, school-age, and adolescent children

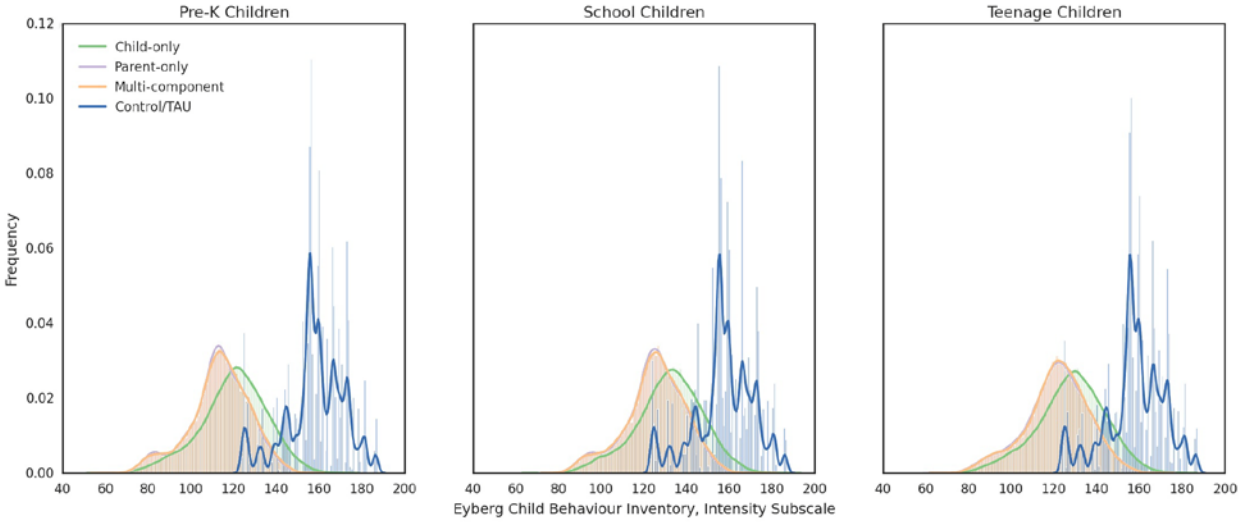


Figure 5. Summary of estimated overall treatment outcomes (ECBI Problem Subscale) in studies of preschool, school-age, and adolescent children

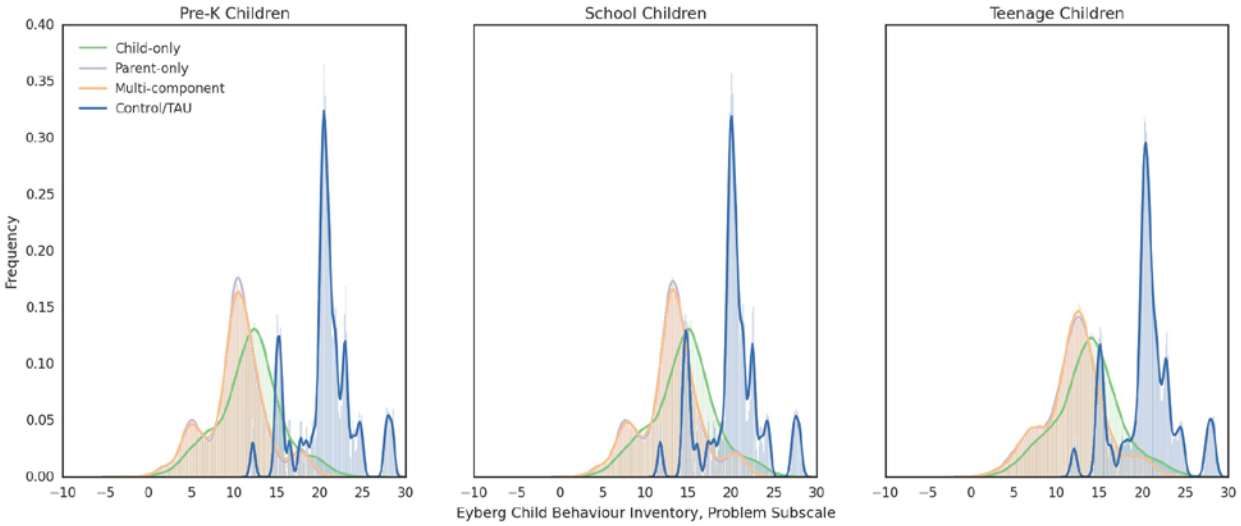
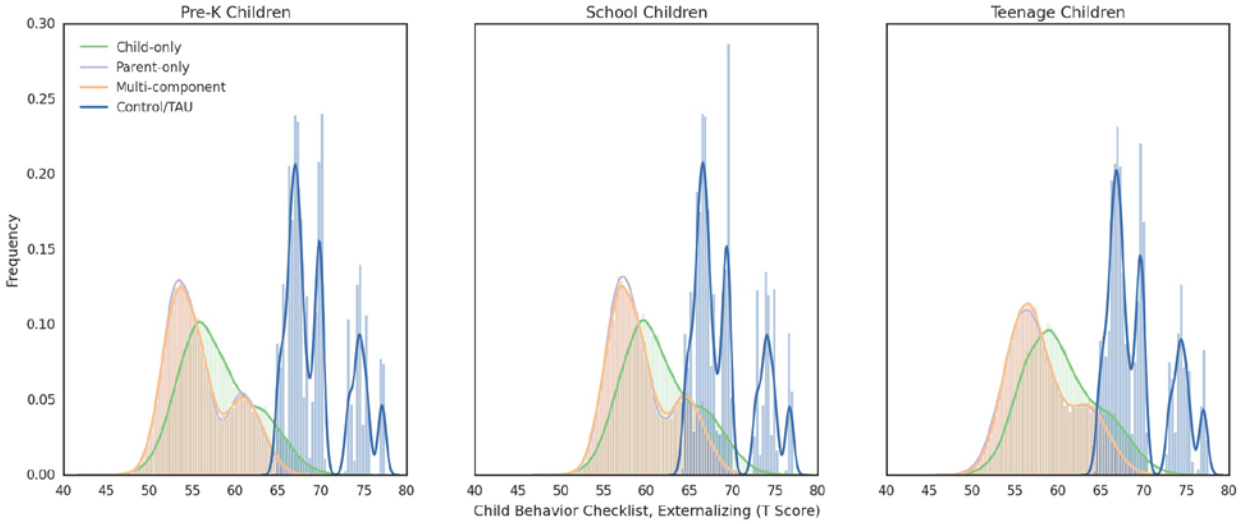


Figure 6. Summary of estimated overall treatment outcomes (CBCL Externalizing T-score) in studies of preschool, school-age, and adolescent children



All three classes show shifts away from control/treatment as usual, though with high residual variability within class, and overlap among classes.

Random effect variances describe additional variation in the output beyond that accounted for by the factors included in the model. Mean estimates were 0.18 (SD: 0.034) (95% CI: 0.12 to 0.25) for ECBI Intensity score, 0.17 (SD: 0.038) (95% CI: 0.09 to 0.24) for ECBI Problem score, and 0.13 (SD: 0.027) (95% CI: 0.08 to 0.18) for CBCL Externalizing T score.

Using cut points greater than 127 for the ECBI Intensity scale, 11 for the ECBI Problem scale, and 60 for the CBCL Externalizing T-score,[174,175] we estimated the marginal posterior probabilities of remaining above the cut point on each measure (Table 30). Remaining above the clinical cut point means that children continued to experience clinically significant symptoms. Posterior probabilities of remaining above the cut point are nominally higher for the treatment as usual/control group relative to each of the intervention groups, with multicomponent interventions showing the lowest proportion of children still above the clinical cut off post-treatment.

Table 30. Posterior probabilities of treatment outcome values being above standard threshold for three instruments (ECBI Intensity, ECBI Problem, CBCL Externalizing T-score) by age group

Instrument	Age Group	Child-Only	Parent-Only	Multicomponent	TAU/Control
ECBI, Intensity Subscale	**Preschool**	0.34	0.16	0.17	0.95
	School	0.66	0.46	047	0.95
	Adolescent	0.56	0.36	0.37	0.95
ECBI, Problem Subscale	**Preschool**	062	0.40	0.42	1
	School	0.82	0.77	0.77	1
	Adolescent	0.78	0.66	0.68	1
CBCL, Externalizing (T-score)	**Preschool**	0.30	0.19	0.19	1
	School	0.59	0.36	0.37	1
	Adolescent	0.48	0.31	0.31	1

ECBI = Eyberg Child Behavior Inventory; CBCL = Child Behavior Checklist; TAU = treatment as usual
Note: Standard threshold values: ECBI, Intensity=127, ECBI Problem=11, CBCL, Externalizing T-score=60

For example, this means that 95 percent of school-age children randomized to TAU/Control interventions, 66 percent of school-age children randomized to interventions with only a child component, 46 percent of school-age children randomized to interventions with only a parent component, and 47 percent of school-age children randomized to multicomponent interventions remained above the clinical ECBI Intensity Subscale clinical cutoff at the end of treatment. This suggests that multicomponent interventions are more effective. Similar trends were evident for the other age groups and outcome measures.

For the PCIT intervention, there was some uncertainty regarding whether it was most appropriately classified as a multicomponent intervention (as shown above) or as an intervention with only a parent component. We classified PCIT as a multicomponent intervention primarily because the focus of the intervention – as its name suggests – is on the parent-child interaction and includes the parent and child engaged together in activities. Thus, PCIT is arguably more similar to the family-based interventions included in our multi-component intervention category than it is to an intervention that only includes parents (e.g., our category of interventions that only include a parent component).

Nevertheless, to address this concern, we ran the model under both classifications (i.e., with PCIT categorized as a multicomponent intervention (as shown above) and as an intervention with only a parent component (results not shown) to compare the resulting estimates). Classifying PCIT as an intervention with only a parent component did not significantly change our meta-analysis results, although point estimates of effect were nominally different.

Key Question 2: In children under 18 years of age treated for disruptive behaviors, are alpha-agonists, anticonvulsants, beta-blockers, central nervous system stimulants, first-generation antipsychotics, second-generation (atypical) antipsychotics, and selective serotonin reuptake inhibitors more effective for improving short-term and long-term psychosocial outcomes than placebo or other pharmacologic interventions?

Overview of the Literature for KQ2

This section presents results of studies meeting our review criteria and addressing the effectiveness of pharmacologic treatments for disruptive behavior. Thirteen studies[176-188] (reported in 15 papers)[176-190] of medical intervention met the criteria for inclusion. Medical studies fall into four major categories; antipsychotic, antiepileptic drugs, typically targeted to aggression in children,[191] and a group of drugs comprising both stimulants and nonstimulants typically used in children with comorbid ADHD (Table 31). Three studies evaluated short-term quality of life outcomes. No studies were of drugs with an FDA indication for DBD.

Table 31. Study characteristics (KQ2)

Characteristic		Antipsychotic	Antiepileptic	Stimulant	Nonstimulant	All
Study design	RCT	4	3	2	3	**12**
	Cohort	1	0	0	0	**1**
Location	USA/ Canada	4	3	2	1	**10**
	Europe	0	0	0	2	**2**
	Australia	0	0	0	0	**0**
	Other	1	0	0	0	**1**
Study Population	Mean age, years	10.7	14.9	10.6	10.1	**11.3**
	Proportion males, %	89	86	79	82	**85**
	Randomized	435	108	391	537	**1471**
	Analyzed[a]	433	105	368	533	**1439**
Outcome Measure[b]	CGI-S	3	2	1	0	**6**
	CGI-I	3	1	1	0	**5**
	OAS	2	3	0	0	**5**
	SNAP-IV	0	0	1	2	**3**
	Connors	2	1	1	1	**5**
	Others	6	6	1	0	**13**
Source of Funding	Industry	3	1	1	3	**8**
	Government	0	0	1	0	**1**
	Mixed	1	2	0	0	**3**
	Not Reported	1	0	0	0	**1**
Risk of Bias	High	2	0	2	1	**5**
	Moderate	2	3	0	2	**7**
	Low	1	0	0	0	**1**
	Total	**5**	**3**	**2**	**3**	**13**

OAS = Overt Aggression Scale; CGI-S = Clinical Global Impressions-Severity-; CGI-I = Clinical Global Impressions-Improvement; SNAP-IV = Swanson, Nolan, and Pelham Rating Scale-Revised

[a]Some studies do not report the number analyzed.

[b]Numbers do not tally as studies could use more than one measure.

Key Points for KQ2

- Thirteen studies (12 RCTs and 1 cohort study) evaluated pharmacologic treatment for DBDs. One RCT was assessed as low risk of bias; seven were assessed as moderate risk of bias, and four as high risk of bias. The one nonrandomized controlled study was assessed as high risk of bias.
- Almost all studies were wholly or partially funded by a pharmaceutical industry. One study was federally funded.
- The duration of studies was short, with a range of 4 to 10 weeks. One study assessed 6 months of maintenance therapy.
- Studies of antipsychotic medications had mixed results over the short term, including differences in clinician versus parent rated outcomes within the same study.
- Valproic acid, an antiepileptic, also showed mixed results in RCTs, with one placebo-controlled study favoring the intervention, and another study demonstrating no significant difference. In one dosing study, higher doses were associated with greater effectiveness than lower doses.
- In one high risk of bias RCT, stimulants were associated with significant improvements in the ODD subscore of the parent-rated SNAP-IV for children and adolescents with ODD who were treated with mixed amphetamine salts extended release at doses of 30 mg/day over 5 weeks compared to placebo; and in one RCT (high risk of bias), use of methylphenidate (up to 60 mg/day in 2 divided doses) over a 5-week period in a school-aged population with CD symptoms found both teacher and parent ratings of CD problems improved compared to placebo
- In studies of nonstimulant ADHD medications, two RCTs (1 high and 1 moderate risk of bias) reported that atomoxetine was more effective than placebo in significantly reducing ODD symptoms as measured by the Swanson, Nolan, and Pelham Rating Scale-Revised (SNAP-IV) ODD subscore. Results were maintained up to 9 weeks among school-aged children with comorbid ADHD and ODD.
- In one moderate risk of bias RCT, guanfacine extended release significantly reduced oppositional symptoms for up to 9 weeks as measured by the CPRS-R:L oppositional subscale scores compared with placebo among children with ADHD and comorbid ODD.

Detailed Analysis

Antipsychotics

We identified five studies that address the use of atypical antipsychotic medications for the treatment of DBDs (Table 32 and Table 33). The most well studied antipsychotic was risperidone, for which there were three RCTs.[181,183,186] In addition, one study compared aripiprazole to ziprasidone[188] and one study compared quetiapine to placebo.[180] These studies were funded by the pharmaceutical company that markets the drug studied, except for the aripiprazole and ziprasidone study, for which funding was not specified, but in which all authors had served on the speaker bureau for those manufacturers.

Risperidone

Three studies compared risperidone to placebo, but under different circumstances.[181,183,186] One compared initial risperidone treatment to placebo, one examined the role of risperidone as

an augmentation to stimulant medication, and the third assessed the role of risperidone as maintenance treatment after initial risperidone treatment.

A low risk of bias RCT[186] measured the effect of risperidone on aggression, as measured by the Ratings of Aggression Against People (RAAP) scale. This study was funded by a combination of NICHD funding and the Janssen Research Foundation, and received low risk of bias scored in all domains. Twenty participants were included with 10 randomized to each arm. The trial lasted 10 weeks and took place at a single U.S. academic medical center outpatient clinic. Participants included 19 male and one female, with a mean age of 9.2 years (range: 6 to 14 years, inclusive). The RAAP score difference from baseline over the final four weeks of the 10-week study was −0.7 for the placebo group and −1.91 for the risperidone group (p=0.0007). In addition, the Clinical Global Impressions-Severity (CGI-S) scale was used as a secondary outcome, and the change was significantly greater for the risperidone group compared to the placebo group (−2.46 vs. −1.06, p=0.01). The average number of tablets was 5.0 (0.4) for patients treated with placebo and 4.1 (0.3) for patients treated with risperidone.

The study of risperidone as augmentation to stimulant was also an RCT (moderate risk of bias).[181] Twenty-five children between the ages of 7 and 12, mostly male (22/25) and with a co-diagnosis of ADHD and symptoms of aggression, were included. The primary measures of aggression were the Children's Aggression Scale, parent (CAS-P) and teacher (CAS-T) versions. Mean dose by the end of the 4-week study was 1.08 mg/day for the risperidone group and 1.04 mg/day for placebo. No significant differences in effect were observed on either version of the CAS or the Clinical Global Impressions (CGI).

Finally, a large multicenter RCT (high risk of bias) examined the role of risperidone as maintenance treatment after an initial 12-week treatment period.[183] Participants were primarily boys, ages 5 to 17 (n = 335) and were randomized to 6 months of risperidone or placebo after an initial 12 weeks of treatment with risperidone. Eligible patients had a *DSM-IV* diagnosis of conduct disorder, ODD, or DBD, not otherwise specified. Outcomes were assessed using the Nisonger Child Behavior rating form, the CGI and CGAS. The study was conducted from 2011-2003 in seven countries in Europe and one country in Africa (S. Africa). During the 6-month maintenance phase of the study, the average risperidone dose was 0.81 mg/day for children less than 50kg and 1.22 mg/day for children who weighed greater than or equal to 50 kg. At the end of the study, Nisonger Child Behavior Rating Form score for Conduct problems increased (worsened) from the end of the acute phase by 5.0 (9.5) points in the risperidone group (n = 172) and by 8.8 (11.2) points in the placebo group (n = 163). The CGI-S increased (worsened) by 0.6 (1.2) in the risperidone group and 1.2 (1.4) in the placebo group. The CGAS decreased (worsened) by 3.5 (12.4) points in the risperidone group and 10.2 (14.5) points in the placebo group. All differences were statistically significant (p<0.001). However, this study is challenged by high attrition, with only 58 percent (100/172) of the treatment group and 38 percent (62/163) of the placebo group completing. Overall, there was little difference between risperidone and placebo in the maintenance treatment.

Table 32. Difference in disruptive behavior for studies of antipsychotic medications

Author, Year Country (N Randomized) Risk of Bias	Group: Intervention [Dose] (N Analyzed)	Outcome (Measure)	Baseline Mean (SD)	Last Followup Mean (SD)	Change from Baseline to Last Followup	Between-Group Difference[a]
Connor DF, et al., 2008[180] United States (19) Moderate	**G1:** Quetiapine [294 (78) mg/d] (9) **G2:** Placebo (10)	Disruptive behavior (CGI-S)	**G1:** 5.9 (0.6) **G2:** 5.5 (1.2)	Study week 7 **G1:** 3.4 (1.1) **G2:** 5.0 (0.6)	**G1**: NR **G2**: NR	**G1 vs. G2:** 1.6 (95% CI: 0.9 to 3.0), p=0.007
Findling RL, et al., 2000[186] United States (20) Low	**G1:** Risperidone [0.028 (0.004) mg/kg/day, range: 0.75 to 1.50 mg/d] (10) **G2:** Placebo (10)	Disruptive behavior (CGI-S)	**G1:** NR **G2:** NR	Study week 10 **G1:** 2.32 (0.50) **G2:** 4.92 (0.68)	**G1:** −2.58 (0.49) **G2:** −0.08 (0.66)	**G1 vs. G2:** p=0.003
Reyes M, et al., 2006[183] Multinational (335) High	**G1:** Risperidone [0.81 (0.34) mg/d;[b] 1.22 (0.36) mg/d[c]] (172) **G2:** Placebo (163)	Conduct Problems (NCBR)	**G1:** NR **G2:** NR	**G1:** NR **G2:** NR	**G1:** 5.0 (9.5) **G2:** 8.8 (11.2)	**G1 vs. G2:** p<0.001
		Disruptive behavior (CGI-S)	**G1:** NR **G2:** NR	**G1:** NR **G2:** NR	**G1:** 0.6 (1.2) **G2:** 1.2 (1.4)	**G1 vs. G2:** p<0.001
		Disruptive behavior (CGAS)[d]	**G1:** NR **G2:** NR	**G1:** NR **G2:** NR	**G1:** −3.5 (12.4) **G2:** −10.2 (14.5)	**G1 vs. G2:** p<0.001

CI=confidence interval; NR=not reported; CGI-S=Clinical Global Impressions-Severity; NCBR=Nisonger Child Behavior Rating Form; CGAS=Children's Global Assessment Scale; mg/d=milligram per day; mg/kg/day=milligram per kilogram per day

[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group. Effect favors G1 unless noted otherwise.

[b] Mean dose during maintenance phase for patients weighing less than 50 kg.

[c] Mean dose during maintenance phase for patients weighing 50 kg or more.

[d] Higher CGAS score indicates improvement.

Table 33. Difference in aggression for studies of antipsychotic medications

Author, Year Country (N Randomized) Risk of Bias	Group: Intervention [Dose] (N Analyzed)	Outcome (Measure)	Baseline Mean (SD)	Last Followup Mean (SD)	Change From Baseline to Last Followup	Between-Group Difference[a]
Bastiaens L, 2009[188] United States (46) High	**G1:** Aripiprazole [range: 2.5 to 5.0 mg/d] (20) **G2:** Ziprasidone [range: 20 to 40 mg/d] (14)	Aggression (OAS)	**G1:** 6.8 (1.8) **G2:** 7.4 (2.1)	**G1:** 2.3 (2.9) **G2:** 3.1 (2.0)	**G1:** −4.5 (p=0.0005) **G2:** −4.3 (p=0.0018)	**G1 vs. G2:** p=NS
Connor DF, et al., 2008[180] United States (19) Moderate	**G1:** Quetiapine [294 (78) mg/d] (9) **G2:** Placebo (10)	Aggression (OAS)	**G1:** 73.2 (34.3) **G2:** 40.4 (23.8)	**G1:** 43.3 (55.6) **G2:** 49.4 (27.8)	NR	**G1 vs. G2:** p=NS

Table 33. Difference in aggression for studies of antipsychotic medications (continued)

Author, Year Country (N Randomized) Risk of Bias	Group: Intervention [Dose] (N Analyzed)	Outcome (Measure)	Baseline Mean (SD)	Last Followup Mean (SD)	Change From Baseline to Last Followup	Between-Group Difference[a]
Findling RL, et al., 2000[186] United States (20) Low	**G1:** Risperidone [0.028 (0.004) mg/kg/d, range: 0.75 to 1.50 mg/d] (10) **G2:** Placebo (10)	Aggression (RAAPP)	**G1:** NR **G2:** NR	Study week 10 **G1:** 2.24 (0.42) **G2:** 3.00 (0.30)	**G1:** −1.65 (0.40) **G2:** −0.16 (0.54)	**G1 vs. G2:** p=0.03
Armenteros JL, et al., 2007[181] United States (25) Moderate	**G1:** Risperidone [1.08 (0.63) mg/d] (12) **G2:** Placebo [1.04 (0.52) mg/d] (13)	Aggression (CAS-P)	**G1:** 12.9 (7.2) **G2:** 12.1 (5.2)	Data shown in figure only	**% improved from baseline** **G1:** 100 **G2:** 77	Effect size **G1:** 7.9 **G2:** 7.4 p=NS
		Aggression (CAS-T)	**G1:** 3.9 (3.6) **G2:** 5.1 (4.5)	**G1:** NR **G2:** NR	**% improved from baseline** **G1:** 27 **G2:** NR	**G1 vs. G2:** p=NS
		Aggression (CGI-S)	**G1:** 4.5 **G2:** 4.5	**G1:** 3.2 **G2:** 3.2	**G1:** NR **G2:** NR	**G1 vs. G2:** p=NS
		Aggression (CGI-I)	**G1:** NR **G2:** NR	NR	**G1:** −1.0 **G2:** −0.5 **% improved from baseline** **G1:** 75 **G2:** 38	**G1 vs. G2:** p=0.06

LSM = least square mean; CI = confidence interval; ND = no data; NR = not reported; OAS = Overt Aggression Scale; CGI-S = Clinical Global Impressions-Severity; CGI-I = Clinical Global Impressions-Improvement; RAAPP = Rating of Aggression Against People and/or Property; CAS-P = Children's Aggression Scale-Parent; CAS-T = Children's Aggression Scale-Teacher; mg/d = milligram per day

[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group.

Aripiprazole Versus Ziprasidone

One nonrandomized, open trial (high risk of bias)[188] measured the difference in effect between aripiprazole and ziprasidone on aggression ratings in a sample of 46 mostly male (36/46) patients between the ages of 6 and 18 at an American outpatient clinic. Patients were eligible for inclusion if they demonstrated clinically significant aggressive behavior, deemed severe enough to warrant pharmacotherapy. Measurements were taken at baseline and after two months of treatment. Participants in both groups had reductions in their scores on the Overt Aggression Scale (OAS). Across groups there was a reduction among completers from 7.1 (1.9) to 2.6 (2.5). There was no difference in effect between the groups. The aripiprazole group had a mean decrease of 4.5 points on the OAS and the ziprasidone group had a mean decrease of 4.3 points on the OAS.

Quetiapine Versus Placebo

One randomized, controlled trial (moderate risk of bias)[180] compared the efficacy of quetiapine versus placebo for reducing aggression, assessed via the parent-rated OAS and clinician-rated CGI. Additional measures were the parent-rated Conners Parent Rating Scale

(CPRS) and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Study participants met criteria for a primary diagnosis of conduct disorder and were documented to have moderate-to-severe aggressive behavior (OAS score ≥ 25) and at least moderate severity of symptoms (CGI-S score ≥ 4).

The study was conducted at a single academic medical center in the United States. Nine patients were randomized to receive quetiapine, and 10 were randomized to receive placebo. Patients were between the ages of 12 and 17, inclusive and were mostly male (14/19). The patients were recruited from a single site and the trial lasted for 7 weeks, including 6 weeks of quetiapine versus placebo. At the end of the study, the average (SD) daily dose of quetiapine was 294 (78) mg. While no difference was observed on the OAS (rated by parents), there was a significant difference in outcomes measured by the CGI (rated by clinicians). The quetiapine group average CGI score fell from 5.9 to 3.4 over six weeks and the placebo group fell from 5.5 to 5.0, for a difference between groups of 1.8 (95% CI: −0.53 to −3.1). The additional measures were CPRS (no significant difference) and Q-LES-Q, which showed an improved quality of life rating for the parents of the children in the quetiapine group (11.3 units) compared with a decrease of 4.1 units in the placebo group (p=0.005). Overall, the results were mixed regarding difference between quetiapine and placebo.

Antiepileptics

Valproic Acid

We identified two independent studies and one related pair of studies that addressed the use of valproic acid in the treatment of disruptive behavior in children (Table 34).[178,184,185,189] These studies were funded by the drug manufacturer, Abbott pharmaceuticals, except for one,[185] which was funded by a grant from the National Institute of Drug Abuse.

Table 34. Difference in disruptive behavior for studies of valproic acid at last followup

Author, Year Country (N Randomized) Risk of Bias	Group: Intervention [Dose] (N Analyzed)	Outcome (Measure)	Baseline Mean (SD)	Last Followup Mean (SD)	Mean Change	Between-Group Difference[a]
Blader et al., 2009[178] United States (30) Moderate	**G1:** Divalproex [567 ± 291 mg/d] (14) **G2:** Placebo (13)	Aggression, retrospective (OAS)	**G1:** 62.13 (42.63) **G2:** 61.54 (28.98)	**G1:** 32.13 (44.14) **G2:** 35.77 (28.86)	**% who met remission criteria** **G1:** 57 **G2:** 15	**G1 vs. G2:** 41.76% difference (95% CI: 10 to 74%)
Donovan et al., 2000[185] United States (20) Moderate	**G1:** Divalproex [750-1500 mg/d] (7) **G2:** Placebo (8)	Aggression symptom improvement (OAS)	**G1:** NR **G2:** NR	**G1:** NR **G2:** NR	**% who improved** **G1:** 86 **G2:** 25	**G1 vs. G2:** p=0.003
Steiner et al., 2003[184] and Padhy et al., 2011[189] United States (71) Moderate	**G1:** Divalproex [1000 mg] (34) **G2:** Divalproex [125 mg] (24)	Disruptive behavior (CGI-I)	**G1:** NR **G2:** NR	**G1:** NR **G2:** NR	**% much improved** **G1:** 53 **G2:** 8	**G1 vs. G2:** p<0.0008

CGI-I = Clinical Global Impressions-Improvement; NS = not significant; OAS = Overt Aggression Scale; mg/d = milligram per day

[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group.

Valproic Acid Versus Placebo

One randomized, placebo-controlled study (moderate risk of bias)[178] measured the effect of valproic acid in reducing aggressive behavior in younger children, from ages 6 to 13 years, with 21 of 27 males, who had aggression persisting after a trial of stimulant medications. Thirty patients were randomized to add-on valproic acid or placebo adjunctive to stimulant medication for eight weeks. The study participants were boys (n = 21) and girls (n = 6) with a diagnosis of ADHD and a co-diagnosis of either ODD or CD. Enrollment occurred between 2004 and 2007 at two academic medical centers in the United States. The mean daily dose of children in the valproic acid group was 567 mg/day (mean serum level: 68.11 mg/liter) and the children assigned to the placebo group had a drug equivalent dose of 685 mg.

The primary outcome was scoring on the Retrospective-Modified Overt Aggression Scale (R-M OAS). Thirteen patients in the placebo group and 14 patients in the valproic acid group were analyzed due to withdrawal prior to first assessment. The scores on the R-M OAS dropped from 41.80 to 32.13 in the valproic acid group and from 53.31 to 35.77 in the placebo group, with no significant difference between groups.

Another placebo-controlled crossover RCT (moderate risk of bias)[185] included children and adolescents, ages 10 to 18, mostly male (16/20) with conduct disorder or oppositional defiant disorder. The study was conducted at an outpatient clinic at an academic medical center in the United States. A blinded assessor rated the modified OAS and the SCL-90 Anger Hostility items. Response was measured as greater than or equal to 70 percent decrease from baseline in the combined scores of these items. The final dose of valproic acid ranged from 750 to 1500 mg per day. In the first 6-week phase of the study, 10 patients were randomized to the valproic acid arm and eight patients responded. None of the 10 patients randomized to the placebo arm responded.

During the second 6-week phase of the study, the participants crossed over to the alternate intervention; six of seven nonresponders to placebo in the initial phase achieved response in the treatment phase. Of the eight who switched from the treatment group to placebo in phase 2, all of whom had responded in phase 1, six relapsed.

High Dose Versus Low Dose Valproic Acid

One moderate risk of bias randomized, placebo-controlled study (reported in two publications)[184,189] measured the effect of valproic acid on a group of adolescent male patients with a diagnosis of conduct disorder from a correctional facility in California. The trial was 7 weeks long with 6 weeks of active treatment. Data were analyzed from 58 completers, all of whom had at least one offense "against persons." The study included a (blinded) clinician-reported CGI. In the high dose group (mode=1000 mg/day, n = 34), 53 percent were "very much or much improved," 29 percent were "minimally improved" and 18 percent were "no change or minimally worse." In the low dose group (mode=125 mg/day, n = 24) 8 percent were "very much or much improved," 42 percent were "minimally improved" and 50 percent were "no change or minimally worse." The second paper of this family[189] focused on the difference between treatment with high or low dose valproic acid on High Distress Conduct Disorder (HDCD) and Low Distress Conduct Disorder (LDCD). In the high dose group, 25 were identified as HDCD and nine with LDCD. Of those with HDCD on high dose valproic acid, 16 showed a response as measured by CGI-I (defined as improved, much improved or very much improved) and nine showed no response (defined as No Response). Of those with HDCD on low dose valproic acid, two were responders and 14 showed no response. Of those with LDCD on high dose valproic acid, two were responders and seven showed no response. Of those with LDCD on low dose valproic acid, none showed response and eight showed no response. Overall,

valproic acid appeared more effective at high dose than low dose, and more effective in the HDCD group than the LDCD group.

Overview of Medications Commonly Used To Treat ADHD

A number of drugs typically used to treat ADHD are also used in the treatment of disruptive behaviors, most often with children who have comorbid ADHD and DBD. They fall into two primary classes: stimulants and nonstimulants.

We identified two studies that evaluated the use of stimulants: methylphenidate[187] and mixed amphetamine salts extended release.[182] We identified three studies (reported in 4 papers) that addressed the use of pharmacologic agents that are nonstimulants: selective norepinephrine reuptake inhibitor atomoxetine[176,179,190] and the central alpha2A-adrenergic receptor agonist guanfacine.[177] All five studies were RCTs and were conducted in Germany,[176] Italy,[179] and the United States.[177,182,187] We rated two as moderate risk of bias, and three as high risk of bias. All studies were conducted among school-aged children (range: 6 to 17 years of age).

All studies provided definitions for ODD/CD/DBD, however, most included populations with comorbid ADHD. For the nonstimulant ADHD medications, the two RCTs of atomoxetine[176,179] (reported in 3 papers[176,179,190]) studied children with ADHD and comorbid ODD, as defined by the DSM-IV-TR. One RCT of guanfacine studied children with ADHD defined by DSM-IV-TR and oppositional symptoms according to the subscale of the Conners Parent rating Scale Long form (CPRS-R:L)."[177] For the ADHD stimulant medications, the RCT of methylphenidate[187] used *DSM-III* criteria for CD with slight modification where two-thirds had comorbid ADHD, as defined by *DSM-IV* criteria. The RCT of amphetamine[182] included children with ODD as defined by *DSM-IV-TR*, 79 percent had comorbid ADHD.

Outcomes efficacy measures for ODD symptoms included either the SNAP-IV ODD subscore or the oppositional subscore of the Conners Parent rating scale. Two papers also reported quality of life.[179,190] The duration of studies was short, ranging from 4 to 9 weeks. Three of the studies were industry sponsored.[176,179,182]

Stimulants Overview

Two studies, one industry-funded[182] and one funded in part by the National Institute of Mental Health,[187] assessed as high risk of bias evaluated the use of two different stimulant medications (amphetamine, methylphenidate) among children with DBD (Table 35).

The first was conducted in the United States and evaluated four different doses of mixed amphetamine salts extended release compared to placebo over a 4-week period among children and adolescents aged 6 to 17 years with ODD as defined by *DSM-IV-TR*.[182] Most (79%) had comorbid ADHD; however, results were not presented separately for this subgroup. The mean age of patients was 10.6 years among those who received mixed amphetamine salts extended release and 10.5 years in the placebo group; 69 percent were male. Significant improvements were observed in the ODD subscale of the SNAP-IV parent rating for doses of 30 mg/day (least squares mean difference from baseline: −0.43) compared to placebo ($p<0.005$).

One RCT (high risk of bias) also conducted in the United States evaluated use of methylphenidate (up to 60 mg/day in 2 divided doses) compared to placebo over a 5-week period among a school-aged population with CD symptoms.[187] Criteria for CD were defined by *DSM-III* with slight modification; two-thirds of the population had comorbid ADHD, as defined by *DSM-IV*. The mean age was 10.2 years in the treatment group and 10.2 years in placebo with 88 and 90

percent proportion of males, respectively. Results found both teacher and parent ratings of CD problems improved compared to placebo.

Table 35. Difference in disruptive behavior for studies of stimulant medications

Author, Year Country (N Randomized) Risk of Bias	Group: Intervention [Dose] (N Analyzed)	Outcome (Measure)	Baseline Mean (SD)	Last Followup Mean (SD)	Mean Change (SD)	Between-Group Difference[a]
Spencer et al., 2006[182] United States (308) High	**G1:** MAS XR [10 mg/d] (58) **G2:** MAS XR [20 mg/d] (56) **G3:** MAS XR [30 mg/d] (64) **G4:** MAS XR [40 mg/d] (59) **G5:** Placebo (60)	ODD Symptoms (SNAP-IV ODD, Parent report)	Baseline data in figures only	Followup data in figures only	**LSM differences** **G1:** −0.23 **G2:** −0.26 **G3:** −0.43 **G4:** −0.30	**G3 vs. G5:** p<0.005 **All treatment groups vs. G5:** p=0.024
	G1: MAS XR [10 mg/d] (30) **G2:** MAS XR [20 mg/d] (31) **G3:** MAS XR [30 mg/d] (34) **G4:** MAS XR [40 mg/d] (27) **G5:** Placebo (30)	ODD Symptoms (SNAP-IV ODD, Teacher report)	**G1:** 1.1 (0.76) **G2:** 1.24 (0.91) **G3:** 0.92 (0.81) **G4:** 1.09 (0.90) **G5:** 0.91 (0.76)	**G1:** 0.66 (0.68) **G2:** 0.72 (0.86) **G3:** 0.45 (0.58) **G4:** 0.68 (0.64) **G5:** 0.95 (0.94)	**G1:** −0.43 (0.77) **G2:** −0.45 (0.91) **G3:** −0.46 (0.57) **G4:** −0.49 (0.78) **G5:** 0.09 (0.62)	**G1 vs. G5:** p=0.047 **G2 vs. G5:** p=0.043 **G3 vs. G5:** p=0.003 **G4 vs. G5:** p=0.059
Klein et al, 1997[187] United States (84) High	**G1:** Methylphenidate hydrochloride [up to 60 mg/d] (36) **G2:** Placebo (35)	Conduct problems overall rating (Connor Teaching Rating scale)	**G1+ G2:** 2.6 (0.7)	**G1:** 1.3 (0.1) **G2:** 2.3 (0.1)	NR	p<0.001

SNAP-IV = Swanson Nolan and Pelham-IV; ODD = oppositional defiant disorder; LSM = least square mean; MAS = mixed amphetamine salts; NR = not reported; XR = extended release; mg/d = milligram per day

[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group.

Amphetamine Salts (Adderall)

One high risk of bias multicenter, randomized, double blind, placebo-controlled study examined the efficacy and safety of mixed amphetamine salts extended release for the treatment of children and adolescents with ODD.[182] Children and adolescents with ODD (n = 308) were randomized 1:1:1:1 to receive active treatment with mixed amphetamine salts extended release 10 mg/day (n = 60), 20 mg/day (n = 58), 30 mg/day (n = 69), or 40 mg/day (n = 61) or placebo (n = 60) for 4 weeks with forced dose escalation after a washout period. Eligible participants were aged 6 to 17 years with ODD as defined by *DSM-IV-TR*. Patients with conduct disorder were excluded. The primary outcome was the ODD subscale of the SNAP-IV parent rating. Secondary outcomes include the ODD subscale of the SNAP-IV teacher ratings, ADHD subscales of the SNAP-IV parent and teacher ratings, the child health questionnaire parent form 50 (CHQ-PF50) and adverse events. A total of 244 patients (79.2%) had comorbid ADHD, however results were not presented among this subgroup. The mean baseline score for the ODD subscale of the SNAP-IV parent rating did not differ by treatment group. In the intention-to-treat

population, statistically significant improvements in oppositional symptoms as measured by the parent-rated SNAP-IV ODD subscale were observed in the least squares mean difference (−0.43) for those in the higher dose (30 mg/day) group compared with the placebo group ($p<0.005$). Statistically significant improvements for the teacher rated ODD subscale of the SNAP-IV from baseline to endpoint was seen in the intention-to-treat populations who received mixed amphetamine salts extended release 10 mg/day ($p=0.047$), 20 mg/day ($p=0.043$), and 30 mg/day ($p=0.003$), compared to placebo group. Mixed amphetamine salts extended release was associated with improvement in quality of life outcomes, measured with the CHQ, including statistically significant improvements in behavior, physical and psychosocial summary for those in the mixed amphetamine salts extended release 30 and 40 mg/day groups compared to placebo; and for self-esteem in the mixed amphetamine salts extended release 40 mg/day group compared to placebo. When stratified by baseline symptoms in a post hoc reanalysis of the per protocol population, mean changes from baseline in the ODD subscore of the parent rated SNAP-IV was greater for the high baseline ODD severity group.

Methylphenidate (Ritalin)

The second stimulant study that we identified compared methylphenidate to placebo in an RCT including 83 children and adolescents with CD.[187] Participants received methylphenidate (n = 41) or placebo (n = 42) for 5 weeks with a maximum dose of 60 mg per day in two divided doses to evaluate symptoms of CD. Eligible participants were 6 to 15 years of age and met *DSM-II* criteria for CD, which were slightly modified; moderate to severe impairment rating by teacher or parents, and an IQ greater than 70. *DSM-IV* criteria were used to diagnose ADHD. Primary outcomes were parent and teacher ratings of CD symptoms based on the Conners Teacher Rating Scale, and subscales of the Quay revised behavior problem checklist, and global estimates of the severity of behavioral problems. Participants mean age was 10.2 (2.3) years in the methylphenidate group and 10.2 (2.5) years in the placebo group. All but two children had at least three symptoms of CD, consistent with *DSM-IV* criteria; 69 percent of the population also met *DSM-IV* criteria for ADHD, however, results were given for the entire sample and not by those with comorbid ADHD separately. Baseline teacher overall rating for conduct problems was 2.6 (0.7). Teacher rated overall conduct problems were significantly less for those children taking methylphenidate [1.3 (0.1)] compared to placebo [2.3 (0.1), $p<0.001$] and factor scores including aggression, conduct problems, and conduct disorder were significantly improved compared to placebo. Teacher ratings of ADHD symptoms were also significantly improved among those who received methylphenidate compared to placebo. Significant improvements on parent ratings of aggression, conduct problems, and conduct disorder were seen in the methylphenidate group compared to placebo. Socialized aggression showed no statistical improvement on either the parent or the teacher ratings. Among 47 elementary school-aged children, classroom observers' ratings showed significant improvements among methylphenidate compared to placebo groups with regards to global rating of conduct problem severity and aggression (Iowa scale).

Nonstimulants

Three studies[176,177,179] reported in four publications[176,177,179,190] evaluated the efficacy of nonstimulants on oppositional symptoms among children with ADHD and ODD symptoms (Table 36). All were RCTs and were conducted in Germany, Italy, and the United States. We assessed risk of bias as moderate in two studies[176,177] and high in one study.[179] All were conducted among school-aged children (range 6 to 17 years of age).

Two RCTs[176,179] addressed the use of atomoxetine in children with ADHD and comorbid ODD/CD. Atomoxetine is a centrally acting, norepinephrine reuptake inhibitor with minimal affinity for other neurotransmitter receptors. Atomoxetine was approved by the FDA for treatment of ADHD in children, adolescents, and adults in 2002.[192] These two RCTs were designed specifically to examine the effects of treatment on oppositional symptoms in children with ADHD and comorbid ODD defined by the *DSM-IV-TR*. The RCTs included 226 participants in treatment arms, and 91 participants in placebo arms. Participants had an average age of 10.9 and 9.7 years in the treatment groups and 11.1 and 10.0 years in the placebo groups of each trial, respectively. More male subjects were included in both treatment (86%, 93%) and placebo groups (81%, 91%) of each trial, respectively. Both trials evaluated doses titrated up to 1.2 mg per kg per day.

Outcome efficacy measures for ODD symptoms were from the SNAP-IV ODD subscore. Mean (SD) baseline SNAP-IV ODD sub-scores were 15.5 (4.4) and 17.2 (NR) in treatment groups and 15.6 (5.1) and 17.5 (NR) in placebo groups for the 2011[176] and 2009[179] studies, respectively. Both RCTs reported significant improvements in ODD symptoms, as measured by either the SNAP-IV ODD subscale or the Conners Parent rating Scale Long (CPRS-R:L) over an 8- to 9-week period. One study[176] reported significant improvement in quality of life in a separate publication[190] and one study[179] found no significant differences in overall quality of life scores over the 8-week period but did find improvements in certain subdomains (risk avoidance, emotional comfort).

We identified one study that evaluated the use of the nonstimulant guanfacine extended release (1-4 mg/day) in children with ADHD and comorbid ODD.[177] ADHD was defined by the *DSM-IV-TR* and oppositional symptoms according to the subscale of the CPRS-R:L form. Guanfacine extended release is a selective central alpha2A-adrenergic receptor agonist indicated for the treatment of ADHD in children ages 6 to 17 years as monotherapy and as adjunctive therapy to stimulant medication. Guanfacine extended release significantly reduced oppositional symptoms as measured by the CPRS-R:L oppositional subscale scores compared with placebo. The duration of all three studies was short, ranging from 8 to 9 weeks. All of the studies were industry sponsored.

Table 36. Difference in disruptive behavior for studies of nonstimulant medications

Author, Year Country (N Randomized) Risk of Bias	Group: Intervention [Dose] (N Analyzed)	Outcome (Measure)	Baseline Score, Mean (SD)	Last Followup Mean (SD)	Mean Change (SD)	Between-Group Difference[a]
Dittmann et al., 2011[176] and Wehmeier et al., 2011[190] Germany (180) Moderate	**G1:** Atomoxetine fast titration [0.5/1.2 mg/kg/day] (44) **G2:** Atomoxetine slow titration [0.5/0.8/1.2 mg/kg/day] (48) **G3:** Placebo (37)	ODD behavior (SNAP-IV ODD)	**G1:** 15.5 (4.1) **G2:** 15.6 (3.8) **G3:** 15.6 (5.1)	% who improved by at least 30% **G1:** 48.3 **G2:** 55.7 **G3:** 35.6	**LSM [95% CI]** **G1:** 8.6 [7.2, 9.9] **G2:** 9.0 [7.7, 10.3] **G3:** 12.0 [10.6, 13.5]	**G1 + G2 vs. G3:** effect size: 0.69, p<0.001 **G1 vs. G2:** effect size: −0.09, p=0.669

Table 36. Difference in disruptive behavior for studies of nonstimulant medications (continued)

Author, Year Country (N Randomized) Risk of Bias	Group: Intervention [Dose] (N Analyzed)	Outcome (Measure)	Baseline Score, Mean (SD)	Last Followup Mean (SD)	Mean Change (SD)	Between-Group Difference[a]
Dell'Agnello et al., 2009[179] Italy (137) High	**G1:** Atomoxetine [0.5/1.2 mg/kg/day] (105) **G2:** Placebo (32)	ODD behavior (SNAP-IV ODD)	**G1:** 17.2 (NR) **G2:** 17.5 (NR)	**G1:** 14.5 (NR) **G2:** 17.2 (NR)	**G1:** −2.7 (4.1) **G2:** −0.3 (2.6)	**G1 vs. G2:** p=0.001
Connor et al., 2010[177] United States (217) Moderate	**G1:** Guanfacine XR [1.0-4.0 mg/d] (136) **G2:** Placebo (78)	ODD symptoms (CPRS-R:L)	**G1:** 19.3 (4.7) **G2:** 19.9 (4.3)	**G1:** NR **G2:** NR	**Least squares mean reduction** **G1:** −10.9 **G2:** −6.8 **Change score %** **G1:** 56.3 **G2:** 33.4	**G1 vs. G2:** Mean change score effect size 0.59, p<0.001 mean % effect size 0.64 p<0.001

SNAP-IV = Swanson Nolan and Pelham-IV; ODD = oppositional defiant disorder; CPRS-R = Conners Parent Rating Scale-Revised; LSM = least square mean; CI = confidence interval; ND = no data; NS = not significant; NR = not reported; XR = extended release; mg/d = milligram per day; mg/kg/day = milligram per kilogram per day

[a] The between-group difference refers to the difference in the change from baseline to last followup between the intervention and comparison group.

Atomoxetine

A moderate risk of bias randomized, double-blind, placebo-controlled, three-arm, multicenter study was conducted in 20 sites in Germany to assess the efficacy of atomoxetine given once daily for 9 weeks (target dose: 1.2 mg/kg/day), using either fast or slow titration, for treating symptoms of ODD in children and adolescents with ADHD and comorbid ODD/CD.[176] Eligible participants were aged 6 to 17 years and met the DSM-IV-TR criteria for ADHD (any subtype) and DSM-IV criteria A through C for ODD; DSM-IV-TR criteria for CD was not an exclusion. Only outpatients were enrolled from primary and secondary sites. Participants were randomized to one of three arms: (1) atomoxetine 0.5 mg/kg/day for 7 days followed by the target dose of 1.2 mg/kg (atomoxetine fast titrating group, n = 60); (2) atomoxetine 0.5 mg/kg/day for 7 days, followed by 0.8 mg/kg/day for 7 days, followed by target does of 1.2 mg/kg/day (atomoxetine-slow titrating group, n = 61); or (3) placebo (n = 59) for nine weeks, after a 3- to 28-day screening and washout period. The primary outcome was the investigator-rated SNAP-IV ODD subscale score. Other outcomes included the SNAP-IV ADHD subscale score and adverse events. Baseline characteristics were comparable for the three groups [84% male, mean age: 11 (3) years]. Participants DBD comorbidity was 74 percent (n = 134) ODD, 24 percent (n = 44) CD, with one patient meeting criteria for DBD, not otherwise specified and one for adjustment disorder. Baseline mean overall SNAP-IV ODD scores were 15.5 (4.35). Using a mixed effects model for repeated measures, treatment with atomoxetine once daily for nine weeks, pooling fast and slow titration arms, significantly reduced ODD symptoms compared to placebo, as measured by the SNAP-IV ODD score, least square mean treatment group difference at week 9, atomoxetine-pooled minus placebo: −3.2 (95% CI: −5.0 to −1.5), effect size: −0.69, p<0.001. The decrease in ODD symptoms was significant for both the fast and slow titration groups, (least square mean, atomoxetine-fast 8.6 (95% CI: 7.2, 9.9), atomoxetine-slow 9.0 (95% CI: 7.7, 10.3)

compared to placebo 12.0 (95% CI: 10.6, 13.5), p<0.001, effects size −0.74 and p=0.003, effect size −0.65, respectively). SNAP-IV ODD scores improved at least 30 percent in 48.3 percent of patients in the atomoxetine fast titration group compared with 55.7 percent in the atomoxetine slow titration group and 35.6 percent in the placebo group. There were no significant differences between the atomoxetine fast and atomoxetine slow titration groups. Atomoxetine significantly reduced ADHD symptoms compared to placebo at week 9 as measured by the SNAP-IV ADHD subscale score. Patients in the atomoxetine slow titration group stayed on treatment significantly longer than did patients in the placebo group (HR=3.57; 95% CI: 1.42 to 8.94, p=0.007). Study was sponsored by industry.

A second paper in the family of studies evaluated the outcome of quality of life in the same 9-week trial of atomoxetine (target dose 1.2 mg/kg/day) versus placebo.[190] Quality of life was measured using the parent rated KINDL-R questionnaire total scores and sub-scores on emotional well-bring, self- esteem, friends, family, school, and physical well- being, a validated instrument. Family burden of illness was measured using the parent rated FaBel questionnaire, a German version of the Impact on Family Scale. At baseline, the mean overall KINDL-R scores were 62.9 (12.78) and the mean overall FaBel score were 53.8 (12.89). Among those treated with atomoxetine, the KINDL-R total score increased significantly compared to those in the placebo group, (mean change: 2.6 vs. −1.6 points) ANCOVA LS-mean difference, atomoxetine pooled minus placebo: 5.0 (0.8, 9.3), effect size: 0.377, p=0.021), which was clinically relevant. There was no significant difference between the fast and slow titration groups in KINDL total or subscores. Quality of life subscores for emotional well- being, self-esteem, family, and friends increased significantly in patients treated with atomoxetine compared to placebo. There were no statistically significant differences in the KINDL-R school subscore; however the subscore on physical wellbeing was significantly worse for patients in the atomoxetine group compared to placebo. Authors felt the physical wellbeing subscore differences may be related to common treatment adverse effects. No significant treatment effects were seen on family burden, as measured by the FaBel total score. However, the FaBel impact on siblings subscore improved significantly more in the atomoxetine group compared to placebo.

Finally, a multicenter, double blind, placebo-controlled trial (high risk of bias) conducted in Italy evaluated the efficacy of atomoxetine over 8 weeks in improving ADHD and ODD symptoms in children and adolescents with ADHD and comorbid ODD who had been non-responders to a previous parent support intervention.[179] Eligible participants were 6 to 15 years of age, who were diagnosed with ADHD and ODD according to *DSM-IV* criteria, and were required to have a score of at least 1.5 SD above the age norm for the ADHD subscale of the SNAP-IV, a CGI-S score of four or higher at screening and baseline, a SNAP-IV ODD subscale score of at least 15, and a normal intelligence score. All patients were provided open-label, parent support for 6 weeks. Patients who did not respond to the parent support phase (response was defined as an improvement in CGI-S score of 2 or more from baseline and at least a 30 percent decrease from baseline in ADHD sub-score of SNAP-IV) were randomized 3:1 to atomoxetine (n = 105) or placebo (n = 32) once daily for 8 weeks.

The atomoxetine dose was titrated from 0.5 mg/kg/day to a target dose of 1.2 mg/kg/day in 7 days. The primary efficacy measure was the ADHD subscale score of the SNAP-IV; the ODD subscale score of the SNAP-IV was a secondary outcome. Other outcome measures included health related quality of life as measured by means of the parent-rated child health and illness profile-child edition (CHIP-CE), and adverse events. Of the 156 patients who participated in the parent support phase, 139 were randomized and 137 were included in the efficacy analysis.

Participants mean age was 9.7 (2.2) years in the atomoxetine arm and 10.0 (2.4) years in the placebo arm; 93 percent were males.

Mean baseline SNAP-IV ODD score was 17.5 for atomoxetine and 17.2 in the placebo arm. At the end of 8 week period the SNAP-IV ODD sub score significantly improved in the atomoxetine group compared to placebo [SNAP-IV ODD subscale score mean change: −2.7 (4.1) in the atomoxetine arm vs. −0.3 (2.6) in placebo arm, p=0.0001]. There was significant decrease in the ADHD subscale of the SNAP-IV in the atomoxetine arm compared to placebo. There was no significant differences between the mean changes of the CHIP-CE total score between atomoxetine (3.6) and placebo (1.2), p=0.071; however the atomoxetine group showed statistically significant differences compared to placebo for the subdomains of risk avoidance (p=0.013) and emotional comfort (p=0.007). The study was sponsored by industry.

Guanfacine (Intuniv)

A moderate risk of bias multicenter randomized, double blind, placebo-controlled trial conducted in the United States randomized children and adolescents with ADHD and oppositional symptoms 2:1 to receive either guanfacine extended release (n = 138) or placebo (n = 79) once daily for 8 weeks.[177] Eligible participants were between 6 and 12 years of age and had a *DSM-IV-TR* diagnosis of ADHD, a baseline score 24 or higher on the ADHD Rating Scale IV, and a baseline score 14 or higher (males) or 12 or higher (females) on the oppositional subscale of the CPRS-R:L. Following a 3-day to 5-week washout, participants underwent a 5-week dose optimization. During optimization, the dose of guanfacine extended release was increased in 1 mg/week increments to a maximum of 5 mg/day based on tolerance, the CGI-S score, and investigator judgment until the optimal dose was identified. Doses were maintained at the optimal level for 3 weeks. The primary outcome was change from baseline to endpoint in the oppositional subscale of the CPRS-R:L. Other outcomes included ADHD-RS-IV criteria, and adverse events. Participant mean age was 9.4 (1.7) years in the guanfacine extended release group and 9.3 (2.0) years in the placebo group. Mean score at baseline on the oppositional subscale of CPRS-R:L was 19.3 (4.74) in the guanfacine extended release group and 19.9 (4.29) in the placebo arm. Distribution of the optimal dose at the endpoint was: 1 mg (5.1%), 2 mg (27.2%), 3 mg (38.2%), and 4 mg (25%).

Guanfacine extended release significantly reduced oppositional symptoms as measured by the parent-rated CPRS-R:L oppositional subscale scores compared with placebo (least-square mean change from baseline: −10.9 for guanfacine extended release and −6.8 for placebo, p<0.001; effect size: 0.59) Least squares mean percentage reductions from baseline were significantly different between guanfacine extended release (56.3%) and placebo (33.4%) groups (effect size: 0.64, p<0.001). Significant reductions were observed in clinician-rated ADHD-RS-IV total scores in those treated with guanfacine extended release compared with placebo.

Key Question 3: In children under 18 years of age treated for disruptive behaviors, what is the relative effectiveness of any psychosocial interventions compared with the pharmacologic interventions listed in Key Question 2 for improving short-term and long-term psychosocial outcomes?

We identified no studies that directly compared psychosocial to pharmacologic interventions for DBD.

Key Question 4: In children under 18 years of age treated for disruptive behaviors, are any combined psychosocial and pharmacologic interventions listed in Key Question 2 more effective for improving short-term and long-term psychosocial outcomes than individual interventions?

We identified no studies assessing the comparative effectiveness of combination interventions.

Key Question 5: What are the harms associated with treating children under 18 years of age for disruptive behaviors with either psychosocial or pharmacologic interventions?

Overview of the Literature for KQ5

Harms for psychosocial interventions were not reported in studies included in KQ1. It is important to note that the absence of data on harms does not mean that harms are not present, even for psychosocial interventions. To represent the potential harms of the drugs used to treat disruptive behaviors in children, we combine data from three sources: 1) prior systematic reviews focused on harms of drugs; 2) empirical data from studies meeting our inclusion criteria for harms assessments; and 3) package insert data available from FDA (briefly summarized here and in more detail in Appendix I).

For each drug class we first summarize existing reviews, then describe the available empirical data from the literature search, and finally present the analysis of harms data gathered from the available gray literature (i.e., package inserts and FDA review packages). Sixteen studies[176-188,193-195] (reported in 18 papers)[176-188,193-197] of medical intervention met the criteria for inclusion and are described below. We included information from three systematic reviews.

The Package Insert Data sections provide an overview of the common and notable adverse events of each medication. When possible, adverse event data specifically from pediatric patients have been included but it should be noted that studies used to develop package inserts were not, of course, limited to the clinical population of interest in this review. Appendix I includes the pediatric indication for medications referenced in the clinical studies included in this review.

For the drug studies, it is important to note that these data often include children using the medications to treat disruptive behaviors and/or other (non-DBD) medical conditions. We summarize the rate of discontinuation due to adverse events as reported in the published studies in Table 37.

Table 37. Participant discontinuation due to adverse events in published studies

Author, Year Study Design: Funding Country	Drugs(s) Number Analyzed	Condition(s) Age, Mean (SD) Years	Discontinuation Due to AEs
Spencer et al., 2006[182] Connor et al., 2005[197](I-C) RCT: Industry United States	Amphetamine 308	ODD 10.6 (2.8)	14 participants in the active treatment groups vs. none in the control group
Bastiaens et al., 2009[188] NRCT: NR United States	Aripiprazole, Ziprasidone 34	DBD 11.9 (2.6)	2 participants on aripiprazole and 6 on ziprasidone
Dittmann et al., 2011[176] (B-P) RCT: Industry Germany	Atomoxetine 180	ODD, CD 11 (3)	8 participants in the active treatment groups (6 in fast titration and 2 in slow titration) vs. 1 in the placebo group
Dell'Agnello et al., 2009[179] RCT: Industry Italy	Atomoxetine 139	ODD 9.9 (NR)	3 participants in the treatment group vs. none in the control group
Steiner et al., 2003[184] (K-P) RCT: Multiple United States	Divalproex 58	CD 15.9 (NR)	NR
Saxena et al., 2010[193] RCT-OL: Multiple United States	Divalproex 40	ODD, CD 13.85 (3.03)[a] 12.75 (3.38)[b]	9 of 20 participants in treatment group did not complete treatment; reasons for discontinuation not given
Blader et al., 2009[178] RCT: Multiple United States	Divalproex 27	ODD, CD, AGG Range: 6 to 13	NR (1 participant in treatment group and 2 in placebo group withdrew)
Donovan et al., 2000[185] RCT: Multiple United States	Divalproex 20	ODD, CD 13.8 (2.4)	1 participant in treatment group and 1 in the placebo group (lack of efficacy)
Connor et al., 2010[177] RCT: Multiple United States	Guanfacine 214	ODD 9.4 (1.84)	14 participants in the active treatment vs. 1 in the placebo group due to AEs; of these 12 in the active treatment vs. none in the placebo group discontinued due to treatment emergent AEs
Klein, et al., 1997[187] RCT: Government United States	Methylphenidate 71	ADHD and CD Range: 6 to 15	4 participants in treatment group and 5 in placebo group left study (reason NR)
Connor et al., 2008[180] RCT: Industry United States	Quetiapine 19	CD, AGG 14.1 (1.6)	1 participant in the treatment group and 7 in placebo group (5 lack of efficacy and 2 protocol violation)
Pandina et al., 2009[196 c] RCT: Industry Multinational	Risperidone 284	DBD 10.8 (2.9)	3 participants in the treatment group vs. 2 in the placebo group
Reyes et al., 2006[183 d] RCT: Industry Multinational	Risperidone 335	CD, ODD, DBD-NOS 11.1 (2.95)	1.7% in the treatment group vs. 0.6% in placebo group
Armenteros et al., 2007[181] RCT: Industry United States	Risperidone 25	ADHD and AGG 7.3 (3.7)	1 participant in treatment group and 1 in placebo (both failed to comply with protocol regulations)

Table 37. Participant discontinuation due to adverse events in published studies (continued)

Author, Year Study Design: Funding Country	Drugs(s) Number Analyzed	Condition(s) Age, Mean (SD) Years	Discontinuation Due to AEs
Findling et al., 2000[186] RCT: Multiple United States	Risperidone 20	CD 9.2 (2.9)	4 participants in treatment group (1 AE and 3 lack of efficacy) vs. 7 in placebo group (4 lack of benefit, 2 noncompliance, 1 LTF)
Ercan et al., 2003[195] [e] OL: Not reported Turkey	Risperidone 20	ODD, CD 10.8 (3.6)	1 participant withdrew because parents believed the child was not benefitting from the treatment.
Penzner et al., 2009[194] [e] NRCT: Government United States	SGA; Stimulant 153	DBD, AGG 11.3 (3)	7.4% in the SGA alone group vs. 4.2% in the SGA plus stimulant groups for intolerance

AGG = aggression; AE = adverse event; ADHD = Attention Deficit Hyperactivity Disorder; CD = conduct disorder; DBD = disruptive behavior disorder; DBD-NOS = disruptive behavior disorder not otherwise specified; N = number; NCT ID = National Clinical Trials Identifier; LTF = lost to followup; ODD = oppositional defiant disorder; OL = open label; RCT = randomized controlled trial; SD = standard deviation; SGA = second generation antipsychotic

[a] treatment group

[b] comparison group

[c] See Reyes et al., 2006[183] for maintenance phase data from the same population

[d] Maintenance phase of the Pandina et al., 2009[196] study

[e] Not in KQ2

Second-Generation Antipsychotics

Risperidone

Key Points

- Studies were generally short-term with the exception of one trial with a 6-month treatment period. Duration of followup post-treatment was minimal in all studies.
- Adverse events were generally considered mild across studies, with weight gain, sedation, and somnolence frequently reported.

Overview

Use of risperidone, a second-generation antipsychotic, for management of disruptive behavior disorders was documented in a limited number of studies (n = 5).[181,183,186,194-196] We rated two RCTs as good quality for harms reporting,[181,186] two as fair,[183,195,196] and one prospective cohort study as good quality for harms reporting.

Systematic Reviews

We identified three good quality systematic reviews addressing harms of atypical antipsychotics in children and adolescents.[49,52,198]

One Cochrane review assessed atypical antipsychotic use in individuals aged 18 years and younger diagnosed with a DBD.[49] Seven of the eight RCTs identified addressed risperidone compared with placebo, and one evaluated quetiapine (summarized below). The primary harms assessed in the review were weight gain and changes in metabolic parameters. Sample sizes in RCTs of risperidone ranged from 13 to 335 (4 studies had 25 or fewer participants), and the review included three of the studies addressed in the current report.[181,186] Mean doses at end of treatment ranged from 0.98 mg per day to 1.5 mg per day. Mean weight gain in the risperidone

group was 2.37 kg more than in the placebo arm over 6 to 10 weeks in a meta-analysis of two trials (mean difference: 2.37, 95% CI: 0.26 to 4.49). Only one study evaluated metabolic changes and reported no clinically significant changes in mean fasting glucose levels during treatment. The investigators considered the overall quality of the evidence addressing these harms to be low.

Another Agency for Healthcare Research and Quality (AHRQ) review included studies of atypical antipsychotics used for any indication in individuals aged 24 years of age and younger.[52] Agents included in studies in the review were haloperidol, risperidone, aripiprazole, olanzapine, pimozide, quetiapine, clozapine, and ziprasidone, and median study duration was 8 weeks. The review evaluated harms by drug class and noted fewer extrapyramidal symptoms associated with olanzapine and risperidone compared with haloperidol (low strength of the evidence), and no significant differences between first and second-generation antipsychotics in prolactin-related adverse events (low strength of the evidence). Risperidone was associated with less dyslipidemia and less weight gain than olanzapine (moderate strength of the evidence). Risperidone was also associated with more prolactin-related harms than olanzapine (moderate strength of the evidence) and with more weight gain than aripiprazole (low strength of the evidence).

Finally, one review and meta-analysis evaluated metabolic and neurologic adverse events associated with second-generation antipsychotic use in children with any mental health disorder and included 35 RCTs (4 reported in the current review).[198] In a meta-analysis of 10 RCTs of risperidone of less than 12 weeks duration, weight gain (mean difference: 1.72 kg, 95% CI: 1.17 to 2.26, $p<0.00001$), prolactin levels (mean difference: 20.70 ng/mL, 95% CI: 16.78 to 24.62, $p<0.00001$), and change in prolactin from baseline to end of treatment (mean difference: 44.57 ng/mL, 95% CI: 32.24 to 56.90, $p<0.00001$) were higher in risperidone groups compared with placebo. The odds of clinically significant weight gain were higher in the risperidone arm compared with placebo (OR=2.90, p=NS) as were the odds of extrapyramidal symptoms (OR=3.35, $p<0.0001$) in the risperidone arm compared with placebo. The review reported no clinically significant changes in laboratory values or blood pressure in seven studies. Blood pressure was elevated in the risperidone group in one study. Olanzapine was associated with greater weight gain than was risperidone in a meta-analysis of two studies (mean difference: 2.41 kg, 95% CI: 0.98 to 3.83, p=0.0009) and with greater BMI change (mean difference: 0.09 kg/m^2, 95% CI: 0.42 to 1.38, p=0.0003). In studies comparing risperidone at different doses or with other agents (pimozide, clonidine, haloperidol), children in the risperidone arms had weight gain and extrapyramidal symptoms that were typically not significantly different from the comparison group, though higher doses of risperidone were associated with greater weight gain and movement symptoms. In a meta-analysis of three RCTs of risperidone versus placebo of more than 12 weeks duration, mean weight gain was higher in risperidone groups compared with placebo (mean difference: 1.95 kg, 95% CI: 1.14 to 2.75, $p<0.00001$). Prolactin levels were higher in the risperidone group versus placebo ($p<0.001$) in one study, as were the odds of extrapyramidal symptoms (OR=3.71, p=NS). The review suggested that risk of metabolic adverse effects is greatest for olanzapine followed by clozapine and quetiapine, while risks were lower for risperidone and aripiprazole. The risk for neurologic harms appeared greatest with risperidone, olanzapine, and aripiprazole.[198]

Summary of Studies Reporting Harms Data

One randomized, double blind, placebo-controlled trial (Reyes 2006) assessed risperidone for maintenance treatment of children and adolescents (mean age: 11.1 years) with disruptive

behavior disorders.[183,196] Patients were eligible to enter the double blind, 6-month maintenance phase of this study after successful treatment with risperidone for a total of 12 weeks. Of the 527 patients who entered the 6-week, open-label, acute treatment phase, five patients did not continue due to adverse effects; in the six-week, single-blind, continuation treatment phase, seven patients discontinued due to adverse effects; finally, during the 6-month maintenance phase, four patients discontinued the study due to adverse effects. Specific adverse effects resulting in discontinuation of study drug were as follows: involuntary muscle contractions, abnormal ECG, paranoid reaction. By the conclusion of the 6-month maintenance phase, 47.7 percent of risperidone-treated patients and 36.2 percent of placebo-treated patients experienced at least one adverse event. The adverse events reported in 5 percent or more of patients are summarized in Table 38. Table 39 summarizes the incidence of extrapyramidal symptoms.

Table 38. Treatment-emergent adverse events occurring in ≥5 percent of participants

Adverse Event	Acute Phase	Continuation Phase	Maintenance Phase	
	Risperidone (n = 527) n (%)	Risperidone (n = 436) n (%)	Risperidone (n = 172) n (%)	Placebo (n = 163) n (%)
Total Adverse Events	289 (54.8)	152 (34.9)	82 (47.7)	59 (36.2)
Headache	59 (11.2)	25 (5.5)	8 (4.7)	11 (6.7)
Rhinitis	22 (4.2)	19 (4.4)	10 (5.8)	9 (5.5)
Upper Respiratory Tract Infection	14 (2.7)	13 (3.0)	13 (7.6)	9 (5.5)
Pharyngitis	11 (2.1)	10 (2.3)	10 (5.8)	4 (2.5)
Abdominal Pain	27 (5.1)	16 (3.7)	6 (3.5)	3 (1.8)
Somnolence	61 (11.6)	10 (2.3)	3 (1.7)	2 (1.2)
Fatigue	55 (10.4)	6 (1.4)	3 (1.7)	0 (0.0)
Increased Appetite	54 (10.2)	9 (2.1)	4 (2.3)	0 (0.0)
Weight Gain	34 (6.5)	6 (1.4)	2 (1.2)	1 (0.6)
Serious Adverse Events	14 (2.7)	2 (0.5)	6 (3.5)	5 (3.1)

Table 39. Treatment-emergent extrapyramidal symptoms

Extrapyramidal Symptom	Acute and Continuation Phases	Maintenance Phase	
	Risperidone (n = 527) n (%)	Risperidone (n = 172) n (%)	Placebo (n = 163) n (%)
Dystonia	5 (0.9)	2 (1.2)	1 (0.6)
Parkinsonism	2 (0.4)	1 (0.6)	0 (0.0)
Akathisia	1 (0.2)	0 (0.0)	0 (0.0)
Tremor	1 (0.2)	0 (0.0)	0 (0.0)
Any EPS Event	8 (1.5)	3 (1.7)	1 (0.6)

EPS = extrapyramidal symptoms

Another publication[196] from the Reyes RCT[183] evaluated the incidence of somnolence in a long-term analysis (6 months) of 284 5 to 17 year old children with DBD receiving risperidone (0.25 to 1.5 mg/day) or placebo.[196] In the initial 6-week phase of the trial, 61 children reported somnolence, while in the 6-week open label phase, 10 participants had somnolence. During the double-blind maintenance phase, three children in the risperidone arm and three in the placebo arm reported somnolence, which was generally considered mild and likely related to risperidone in two of the children in the treatment arm and to placebo in one child in that arm. The mean

(SD) duration of somnolence was 34.3 (42) days in the risperidone and 42.3 (50) days in the placebo arm.

Adverse events reported in a 12-week RCT of risperidone compared with placebo[186] [n = 20 with CD or ODD, mean age: 9.2 (2.9) years] were generally mild and transient and included rash, increased appetite, sedation, headache, and irritability (Table 40). Predicted weight gain (based on repeated measures analysis) was greater in the risperidone group compared with placebo [4.2 (0.7) kg vs. 0.74 (0.9) kg, p=0.003]. No participants had dystonia and dyskinesia. One participant in the risperidone arm withdrew from the study due a rash that subsequently resolved. We rated this study as good quality for harms reporting.

Another short-term (8 weeks) RCT[181] compared risperidone for treatment-resistant aggression in children with ADHD [n = 12, mean age: 7.3 (3.7) years] with placebo [n = 13, mean age: 8.8 (3.1) years].[181] Nineteen children also had CD or ODD diagnoses, and 25 were receiving concomitant stimulants. More children in the placebo group (76.9%) reported an adverse event than in the risperidone group (58.3%, p=NR). Only abdominal pain and vomiting occurred in greater than 10 percent of participants in the risperidone group, while vomiting and somnolence occurred in more than 10 percent of the placebo arm. Weight gain did not differ significantly between groups, and laboratory values remained within normal limits in both groups. Investigators considered adverse events as mild in intensity, and no participants withdrew due to adverse events. Table 40 lists the harms reported by group. We considered this study as good quality for harms reporting.

Table 40. Harms in additional studies of risperidone reporting per participant incidence

Author, Year Design (Quality)	Groups [dose] (N at Final Analysis)	Harms in Treatment Group: n (%)	Harms in Comparison Group, n (%)
Findling et al., 2000[186] RCT (Good)	**G1:** Risperidone (mean 0.028 ± 0.004 mg/kg/day), 6 **G2:** Placebo, 3	Increased appetite: 3 Sedation: 3 Headache: 1 Initial insomnia: 1 Restlessness: 1 Irritability: 1 Enuresis: 0 Nausea/emesis: 1 Rash: 1	Increased appetite: 0 Sedation: 2 Headache: 1 Initial insomnia: 0 Restlessness: 0 Irritability: 0 Enuresis: 1 Nausea/emesis: 1 Rash: 0
Armenteros et al., 2007[181a] RCT (Good)	**G1:** Risperidone (mean 1.08 ± 0.63), 12 **G1:** Placebo, 13	Abdominal pain: 3 (25) Vomiting: 2 (16.7) Somnolence: 1 (8.3) Agitation: 1 (8.3) Increased appetite: 1 (8.3)	Abdominal pain: 1 (7.7) Vomiting: 3 (23.1) Somnolence: 1 (15.4) Agitation: 0 Increased appetite: 0

[a] Study reports harms occurring in 5 percent or more participants.

In one fair quality, 8-week open label trial of risperidone [final dose, mean: 1.27 (0.42) mg/day] including 21 children with ODD or CD and ADHD [mean age: 10.8 (3.6) years], reported side effects were similarly mild.[195] All children had initial mild sedation, and sleep duration increased by a mean of 0.9 hours on parental observation (range 0-3 hours). Mean weight gain was 1.6 (1.9) kilograms (mean 4% increase). Three participants gained more than 10 percent of their baseline body weight, and one gained approximately 29 percent. No participants developed EPS or had abnormal laboratory values.

One good quality analysis of data on participants (ages 4-19, mean 11.3 years) with ODD or CD enrolled in a cohort study of antipsychotic treatments reported specifically on metabolic adverse effects.[194] Participants received antipsychotics either with stimulants (n = 82) or without

stimulants (n = 71). Most of the 153 participants received either risperidone (33.3%) or aripiprazole (29.4%). The most commonly used stimulants were methylphenidate (13.1%) and D-Amphetamine (10.5%), and participants differed on multiple characteristics at baseline (ADHD comorbidity, use of stimulants prior to study, baseline weight at normal or below normal levels, waist circumference). In analyses controlling for baseline differences, changes in body composition, glucose and lipid parameters, and prolactin levels did not differ between groups, nor did discontinuation rates (4.2% in antipsychotics plus stimulant group vs. 7.4% in the antipsychotics alone arm).

Package Insert Data

Adverse event data for risperidone were gathered from the package insert and FDA approval packages for adolescent use.[199] The other FDA review documents available did not include pediatric data.

Adverse events referenced in the warnings/precautions section of the package insert include: parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, weight gain, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain. [199,200]

When assessing the use of risperidone (0.5-6 mg/day) across all pediatric indications (i.e. schizophrenia, bipolar mania, autistic disorder), the mean change in fasting glucose from baseline was 2.6 mg/dL (n = 135), cholesterol was 0.3 mg/dL (n = 133), LDL was 0.5 mg/dL (n = 22), HDL was −1.9 mg/dL (n = 22), triglycerides was 2.6 mg/dL (n = 138), weight was 2 kg (n = 448), and weight gain (more than7% increase) was 32.6% (n = 448).[199,201] Prolactin levels have also been shown to increase from baseline in pediatric patients taking risperidone; which appeared to be dose-dependent relationship.[202] This increase has been shown to lead to prolactin-related adverse events such as: lactation nonpuerperal and ejaculation disorder.[202] Common adverse events reported in long-term studies (greater than 6 months) included weight gain and psychosis.[202] In general, extrapyramidal symptoms, dizziness, somnolence, and increasing salivation, and increased prolactin levels were considered dose-related.[202]

The sponsor conducted a literature search, which uncovered safety data from 206 articles in pediatric patients taking risperidone at doses between 0.25 and 12 mg/day or 0.01 and 0.06 mg/kg/day for up to 7 years.[202] The most frequently reported adverse events were weight gain (75 articles), sedation (47 articles), and extrapyramidal symptoms (32 articles).[202] The most common reasons for discontinuation in these articles included: weight gain (18 articles), extrapyramidal symptoms (11 articles), hyperprolactinemia (8 articles), and sedation (7 articles).[202] Serious adverse events reported in 19 patients included: neuroleptic malignant syndrome (9), tardive dyskinesia (4), pancreatitis (2), acute dystonia (1), probably viral encephalitis (1), worsening mitochondrial disorder (1), and increased carbamazepine level (1).[202]

Common adverse events reported in pediatric patients with schizophrenia taking risperidone 1 to 3 mg/day (n = 55) for 6 weeks included: sedation (24%), parkinsonism (16%), tremor (11%), akathisia (9%), dizziness (7%), dystonia (2%), and anxiety (7%).[199] In patients taking risperidone 4 to 6 mg/day (n = 51) for 6 weeks the following adverse events were reported: salivary hypersecretion (10%), sedation (12%), parkinsonism (28%), tremor (10%), akathisia (10%), dizziness (14%), dystonia (6%), and anxiety (6%).[199,200]

Patients taking risperidone (n = 106) in clinical trials discontinued treatment due to dizziness (2%), somnolence (1%), sedation (1%), lethargy (1%), anxiety (1%), balance disorder (1%), hypotension (1%), and palpitation (1%).[199]

Other Second-Generation Antipsychotics

Key Points

- Two small, short-term studies addressed quetiapine, aripiprazole, or ziprasidone.
- Adverse events were more frequent in the placebo arm in an RCT comparing quetiapine and placebo, and sedation was frequently reported in both arms in a study comparing aripiprazole and ziprasidone.

Overview of the Literature

Aripiprazole, ziprasidone, and quetiapine were used in the management of disruptive behavior disorders in two studies (1 good[180] and 1 poor quality[188] for harms) meeting our criteria.

Systematic Reviews

The good quality Cochrane review of atypical antipsychotics for DBD[49] (described above) included one RCT of quetiapine[180] (described in KQ2 above for effectiveness and below for harms). The Cochrane review addressed the adverse effects of weight gain and metabolic changes as primary outcomes and provided no significant analysis of the limited harms data in the study.

One AHRQ-funded review (described above) addressed atypical antipsychotics including quetiapine.[52] The review reported that quetiapine was associated with significantly less weight gain than olanzapine (moderate strength of the evidence) but with more weight gain when compared with aripiprazole (low strength of the evidence). Quetiapine was also associated with more dyslipidemia than aripiprazole (low strength of the evidence). Aripiprazole was associated with fewer prolactin-related adverse events than placebo (moderate strength of the evidence), and differences between the effects of second generation antipsychotics related to extrapyramidal symptoms, insulin resistance, and sedation were not significant (low strength of the evidence).

Finally, one review and meta-analysis evaluated metabolic and neurologic adverse events associated with second-generation antipsychotic use in children with any mental health disorder. The review included 35 RCTs, four of which are in this review.[198] In a meta-analysis of three studies of quetiapine versus placebo (including the RCT[180] described below), weight gain but not prolactin levels was significantly higher in the quetiapine group (mean difference: 1.41 kg, 95% CI: 1.01 to 1.81). Triglyceride levels, blood pressure, and heart rate were significantly elevated in the quetiapine group compared with placebo in one RCT. The review also included nine RCTs assessing aripiprazole, five of which were combined in meta-analyses. Mean weight gain (mean difference: 0.85 kg, 95% CI: 0.57 to 1.13, $p<0.00001$) and BMI increase (mean difference: 0.27 kg/m^2 95% CI: 0.11 to 0.42, $p=0.0007$) were higher in aripiprazole groups compared with placebo, and the odds of weight gain were significantly higher in the treatment group (OR=3.66, $p=0.0003$). Lipids and ECG values did not differ significantly between groups, and prolactin levels were significantly lower in treated participants versus those in placebo arms at endpoint (mean difference: −5.03 ng/mL, 95% CI: −7.80 to −2.26, $p=0.0004$). Participants receiving risperidone had greater odds of developing extrapyramidal symptoms compared with placebo (OR=3.70, $p<0.00001$). Studies included in the review did not report significant changes in blood

pressure, heart rate, or laboratory values, and only one short-term study addressed ziprasidone. The review suggested that risks of metabolic adverse effects are greatest for olanzapine followed by clozapine and quetiapine, while risks were lower for risperidone and aripiprazole. The risk for neurologic harms appeared greatest with risperidone, olanzapine, and aripiprazole.

Summary of Studies Reporting Harms Data

One good quality, 7-week RCT (Connor 2008) compared quetiapine and placebo in children with CD and moderate-to-severe aggressive behavior (n = 19 [11 completers], mean age overall: 14.1 years).[180] The mean number of parent-reported side effects and the mean severity did not differ significantly between groups nor did child-reported side effects including sedation, social withdrawal, and weight gain. Three adverse events were reported significantly more often by parents of children in the placebo arm compared with quetiapine: decreased mental alertness (n = 9 in placebo arm vs. n = 3 in quetiapine, p=0.01), diminished emotional expression (n = 7 in placebo arm vs. n = 1 in treatment, p=0.009), and diminished facial expression (n = 6 in placebo arm vs. n = 1 in treatment, p=0.03). Weight gain and prolactin levels did not differ significantly between groups, and laboratory parameters were in normal levels in both groups. Children in the quetiapine group had a higher resting pulse than did children in the placebo arm (p=0.01), and one child in the quetiapine group withdrew due to clinically noticeable akathisia. Table 41 lists harms reported by group.

In a poor quality, open label, nonrandomized study,[188] investigators assessed harms following 8 weeks of either aripiprazole [n = 24, (20 completers)] or ziprasidone [n = 22 (14 completers)] in children (mean age: 11.9 years) with aggressive behavior.[188] Use of stimulant medication was allowed (8% of the aripiprazole group; 36% of the ziprasidone group). Overall 71 percent of study completers experienced harms. Reported harms included sedation (n = 10 in aripiprazole arm vs. n = 8 in ziprasidone arm) and nausea and headaches (reported in 2 participants in each arm). Six children in the ziprasidone arm and two in the aripiprazole arm discontinued the study due to sedation. Table 41 lists harms reported by group.

Table 41. Harms reported in studies of other second-generation antipsychotics

Author, Year Study Design Quality	Groups (Final Dose), N at Final Analysis	Harms in Treatment Group, n (%)	Harms in Comparison Group, n (%)
Connor 2008[180] [a] RCT (Good)	**G1:** Quetiapine (range 200-600 mg/d), 8 **G2:** Placebo, 3	Irritability: 7 (78) Restlessness: 7 (78) Sedation: 6 (67) Agitation: 6 (66) Anxiety: 6 (66) Pacing: 4 (44) Social withdrawal: 4 (44) Decreased energy: 3 (33) Decreased mental alertness: 3 (33) Weight gain: 3 (33) Drooling: 2 (22) School refusal: 2 (22) Diminished emotional expression: 1 (11) Diminished facial expression: 1 (11) Muscle stiffness: 1 (11) Overeating: 1 (11) Tremor: 0 (0)	Irritability: 8 (80) Restlessness: 7 (70) Sedation: 9 (90) Agitation: 9 (90) Anxiety: 7 (70) Pacing: 5 (50) Social withdrawal: 5 (50) Decreased energy: 5 (50) Decreased mental alertness: 9 (90) [b] Weight gain: 1 (10) Drooling: 0 (0) School refusal: 4 (40) Diminished emotional expression: 7 (70) [b] Diminished facial expression: 6 (60) [b] Muscle stiffness: 2 (20) Overeating: 2 (20) Tremor: 3 (30)

Table 41. Harms reported in studies of other second-generation antipsychotics (continued)

Author, Year Study Design Quality	Groups (Final Dose), N at Final Analysis	Harms in Treatment Group, n (%)	Harms in Comparison Group, n (%)
Bastiaens 2009[188,203] Open label nonrandomized trial (Poor)	**G1**: Aripiprazole (4.5 ± 2.3 mg), 20 **G2**: Ziprasidone 42.9 ± 18.0 mg), 14	**Aripiprazole** Sedation: 10 (50) Extrapyramidal: 2 (10) Dizziness: 2 (10) Nausea: 2 (10) Headaches: 2 (10) Weight gain: 2 (10) Blurry vision: 0 Agitation: 0	**Ziprasidone** Sedation: 8 (57) Extrapyramidal: 0 Dizziness: 4 (29) Nausea: 2 (14) Headaches: 2 (14) Weight gain: 0 Blurry vision: 2 (14) Agitation: 2 (14)

mg/d = milligram per day; mg = milligram; N = number; G = group; RCT = randomized controlled trial
[a]Parent-reported harms
[b]significantly greater in placebo group, p ≤0.03

Package Insert Data

Aripiprazole

The adverse event data for aripiprazole have been gathered from the package insert as well as FDA approval document for the pediatric schizophrenia indication.[204] Adverse events referenced in the warnings/precautions section of the package insert include: neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia/diabetes mellitus, dyslipidemia, body weight gain, orthostatic hypotension, leukopenia, neutropenia, agranulocytosis, seizures, cognitive motor impairment, suicide, and suicidal ideation.[205]

Pediatric patients (n = 920), aged 6 to 17 years, being treated with aripiprazole for schizophrenia, bipolar mania, or autistic disorder were included in clinical trials that assessed safety.[205] Of these patients, 117 were treated for at least 1 year and 465 were treated for at least 180 days.[205] Adverse events reported in these trials with a frequency of more than 10 percent included: somnolence, headache, vomiting, extrapyramidal disorder, fatigue, increased appetite, insomnia, nausea, nasopharyngitis, and weight increased.[205]

Quetiapine

The harms data provided for quetiapine have been gathered from the package insert and FDA approval documents.[206,207] Only FDA review documents for quetiapine immediate release were assessed. Review documents and adverse event data for quetiapine extended release were not included. The only FDA approval document that contained pediatric harms data was the document assessing QTC prolongation.[206]

Adverse events referenced in the warnings/precautions section of the package insert include: suicidal thoughts and behaviors, neuroleptic malignant syndrome, hyperglycemia, dyslipidemia, weight gain, tardive dyskinesia, hypotension, increased blood pressure, leukopenia, neutropenia and agranulocytosis, cataracts, hypothyroidism, hyperprolactinemia, and cognitive motor impairment.[207]

Ziprasidone

Ziprasidone is not FDA approved for use in pediatric patients and therefore safety data in this population are not available.[208] Since pediatric adverse events were not represented in any FDA approval document for this medication, information from these reviews has not been included.

Divalproex/Valproate

Key Points

- Three small, short-term RCTs (1 fair and 2 poor quality for harms) addressed divalproex and reported harms including sleep changes, irritability and mood changes, gastrointestinal upset, and appetite changes.

Overview

Data on harms of valproate were available from three small RCTs and FDA packaging.

Systematic Reviews

We found no systematic reviews assessing harms of divalproex.

Studies Reporting Harms Data

We rated one 8-week RCT[178] as fair quality for harms reporting, and two RCTs[184,185] as poor quality. The fair quality RCT compared divalproex and placebo in 27 children with stimulant-resistant aggression and ADHD and either CD or ODD.[178] Because divalproex was given as add-on therapy with stimulants, many of the reported adverse effects such as anxiety, nail biting, and appetite suppression were attributed to stimulant use. Trends toward a higher rate of treatment-emergent sadness (divalproex: 3 of 14, 20%; placebo: 0 of 13, 0%; p=0.07) and delayed sleep onset (divalproex: 5 of 14, 36%; placebo: 1 of 13, 8%; p=0.08) were noted but not statistically significant. Table 42 outlines reported harms.

One 7-week RCT of 58 adolescent male patients (age 14-18 years) with conduct disorder compared high (500-1500 mg/day) and low (125 mg/day) doses of divalproex.[184,209] The only adverse effects reported were gastrointestinal upset (n = 1) and sleepiness (n = 6) (Table 42). Side effects typically disappeared within 4 weeks. Another 6-week RCT comparing a dose of 750 to 1500 mg/day of valproex with placebo in children with CD or ODD reported increased appetite in four (20%) of the 20 participants (ages 10 to 18 years) (Table 42).[185]

Table 42. Harms reported in studies of divalproex

Author, Year Design (Quality)	Group [Dose] (N at Final Analysis)	Harms in Treatment Group, n (%)[a]	Harms in Comparison Group, N (%)
Blader et al., 2009[178] RCT (Fair)	**G1:** Divalproex [20 mg/kg] (14) **G2:** Placebo (13)	Insomnia: 7 (50) Crying: 5 (36) Irritability: 5 (36) Anxiety/nervousness: 3 (21) Sadness: 3 (21) Appetite changes: 2 (14) Early waking: 2 (14) Fingernail biting: 2 (14) Nightmares: 2 (14) Overly talkative: 2 (14) Restlessness: 2 (14) Stares into space: 2 (14) Enuresis: 1 (7) Lack of interest: 1 (7) Less talkative: 1 (7) Low energy: 1 (7) Shaking: 1 (7) Tics: 1 (7) Tremors: 1 (7)	Crying: 4 (31) Irritability: 4 (31) Insomnia: 2 (15) Overly talkative: 2 (15) Restlessness: 2 (15) Anxiety/nervousness: 1 (8) Bruises easily: 1 (8) Enuresis: 1 (8) Fingernail biting: 1 (8) Rash: 1 (8)

Table 42. Harms reported in studies of divalproex (continued)

Author, Year Design (Quality)	Group [Dose] (N at Final Analysis)	Harms in Treatment Group, n (%)[a]	
Steiner et al., 2003[184] RCT (Poor)	**G1:** Divalproex, high dose [500-1500 mg/d] (34) **G2:** Divalproex, low dose [125 mg/d] (24)	**G1 + G2:** Increased sleepiness: 6 (10) Nausea and vomiting: 1 (2)	
Donovan et al., 2000[185] RCT (Poor)	**G1:** Divalproex [750-1500 mg/d] (10) **G2:** Placebo (10)	Increased appetite: 4 (20)	None reported

mg/d = milligram per day; RCT = randomized controlled trial; G = group; N = number

[a] There were no reported instances of these harms in the divalproex group: abdominal pain, bruises easily, constipation, dizziness, dry mouth, headache, other (not defined), rash, stomach ache, heart racing, tiredness, trouble walking, unusually happy; and in the placebo group: abdominal pain, bruises easily, constipation, dizziness, dry mouth, headache, other, rash, stomach ache, hear racing, tiredness, trouble walking, unusually happy.

Package Insert Data

The safety information for divalproex sodium was obtained from the package insert.[210] FDA review documents were not available for this medication. Adverse events referenced in the warnings/precautions section of the package insert include: suicidal behavior or ideation, thrombocytopenia, hyperammonemia, hyperammonemic encephalopathy, hypothermia, hepatotoxicity, and pancreatitis.[211] It is important to note that there is an increased risk of developing fatal hepatotoxicity in patients less than two years of age.[210] Specifically in pediatric clinical trials, consisting of 76 patients aged 10-17 years taking divalproex extended release for mania and 231 patients aged 12 to 17 years taking divalproex extended release for migraine, common adverse events (reported >5% and twice the rate of placebo) included: nausea, upper abdominal pain, somnolence, increased ammonia, gastritis and rash.[210]

According to the package insert, divalproex safety and tolerability in pediatric patients is similar to what has been observed in adults.[210] Therefore, the adverse events reported below were not specified for pediatric patients but are included due to the similarity in pediatric safety response. These events are designated by indication.

The following adverse events were reported 89 patients being treated with divalproex for mania: nausea (22%), somnolence (19%), dizziness (12%), vomiting (12%), accidental injury (11%), asthenia (10%), abdominal pain (9%), dyspepsia (9%), and rash (6%).[210] Adverse events occurring at an incidence rate of greater than 1 percent (no more that 5%), in patients taking divalproex included: chest pain, chills, chills and fever, fever, neck pain, neck rigidity, hypertension, hypotension, palpitations, postural hypotension, tachycardia, vasodilation, anorexia, fecal incontinence, flatulence, gastroenteritis, glossitis, periodontal abscess, ecchymosis, edema, peripheral edema, arthralgia, arthrosis, leg cramps, twitching, abnormal dreams, abnormal gait, agitation, ataxia, catatonic reaction, confusion, depression, diplopia, dysarthria, hallucinations, hypertonia, hypokinesia, insomnia, paresthesia, reflexes increased, tardive dyskinesia, thinking abnormalities, vertigo, dyspnea, rhinitis, alopecia, discoid lupus erythematosus, dry skin, furunculosis, maculopapular rash, seborrhea, amblyopia, conjunctivitis, deafness, dry eyes, ear pain, eye pain, tinnitus, dysmenorrhea, dysuria, and urinary incontinence.[210]

The clinical trials used to gather the following adverse events included patients on other antiepilepsy medications.[210] Therefore, it is impossible to clearly state if the following reactions are due to divalproex alone in patients with epilepsy.[210]

Treatment emergent adverse events reported in 77 patients taking divalproex as adjunctive therapy for the treatment of complex partial seizures included: headache (31%), asthenia (27%), fever (6%), nausea (48%), vomiting (27%), abdominal pain (23%), diarrhea (13%), anorexia (12%), dyspepsia (8%), constipation (5%), somnolence (27%), tremor (25%), dizziness (25%), diplopia (16%), amblyopia/blurred vision (12%), ataxia (8%), nystagmus (8%), emotional lability (6%), thinking abnormal (6%), amnesia (5%), flu syndrome (12%), infection (12%), bronchitis (5%), rhinitis (5%), alopecia (6%), and weight loss (6%).[210]

In a controlled trial assessing the use of high dose divalproex (n = 131) as monotherapy for the treatment of complex partial seizures the following adverse events were reported: asthenia (21%), nausea (34%), diarrhea (23%), vomiting (23%), abdominal pain (12%), anorexia (11%), dyspepsia (11%), thrombocytopenia (24%), ecchymosis (5%), weight gain (9%), peripheral edema (8%), tremor (57%), somnolence (30%), dizziness (18%), insomnia (15%), nervousness (11%), amnesia (7%), nystagmus (7%), depression (5%), infection (20%), pharyngitis (8%), dyspnea (5%), alopecia (24%), amblyopia/blurred vision (8%), and tinnitus (7%).[210]

In controlled trials encompassing 358 patients treated with divalproex for complex partial seizures the following adverse events were reported in greater than 1 percent of patients but no more than 5 percent: back pain, chest pain, malaise, tachycardia, hypertension, palpitation, increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess, petechia, SGOT increased, SGPT increased, myalgia, twitching, arthralgia, leg cramps, myasthenia, anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder, sinusitis, cough increased, pneumonia, epistaxis, rash, pruritus, dry skin, taste perversion, abnormal vision, deafness, otitis media, urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, and urinary frequency.[210]

Stimulants

Key Points

- One short-term RCT of methylphenidate reported sleep delay as a harm while an RCT of mixed amphetamine salts including more than 300 children reported harms including insomnia and anorexia.

Overview

Two short-term (≤ 5 weeks), placebo-controlled RCTs of poor quality for harms reporting addressed the safety of mixed amphetamine salts (Adderall®) in the management of ODD[182,197] or methylphenidate for CD.[187]

Systematic Reviews

We did not identify any systematic reviews addressing harms of these agents.

Summary of Studies Reporting Harms Data

The RCT of methylphenidate in patients with conduct disorder[187] did not describe assessment of adverse events, and the specific types of events were not detailed in the results though the study noted that adverse effects occurred in 84 percent of those receiving methylphenidate and in 46 percent of those receiving placebo. The authors also noted that "only a few instances of delayed sleep with medication were severe."[187]

In a dose-escalation study of mixed amphetamine salts in 308 6 to 17 year olds with ODD, adverse events were typically considered mild, though five participants in the treatment arm reported six severe events (arthrosis, hyperkinesias, insomnia, nervousness, pharyngitis, and one suicide attempt).[182,197] Fourteen participants in the treatment arm withdrew from the study due to decreased appetite or insomnia. Table 43 outlines harms occurring in at least 5 percent of patients. Mean decrease in weight was significantly greater in the treatment arm compared with control (range: 1.1 to 3.3 pounds across dosage groups from baseline to endpoint).

Table 43. Adverse events reported in ≥5 percent of patients receiving extended-release mixed amphetamine salts or placebo

Adverse Event n (%)	Mixed Amphetamine Salts				Placebo
	10 mg (n = 60)	20 mg (n = 58)	30 mg (n = 69)	40 mg (n = 61)	(n = 60)
Anorexia	10 (16.7)	22 (37.9)	22 (31.9)	21 (34.4)	3 (5.0)
Insomnia	8 (13.3)	14 (24.1)	16 (23.2)	17 (27.9)	5 (8.3)
Headache	11 (18.3)	10 (17.2)	11 (15.9)	16 (26.2)	9 (15.0)
Abdominal Pain	7 (11.7)	6 (10.3)	10 (14.5)	7 (11.5)	3 (5.0)
Weight Loss	2 (3.3)	6 (10.3)	8 (11.6)	9 (14.8)	0 (0)
Mean Weight Change (kg)[a]	-0.5	-1.6	-1.5	-1.5	0.3
Pharyngitis	6 (10.0)	3 (5.2)	2 (2.9)	7 (11.5)	3 (5.0)
Nervousness	3 (5.0)	4 (6.9)	5 (7.2)	5 (8.2)	0 (0)
Emotional Liability	2 (3.3)	3 (5.2)	6 (8.7)	3 (4.9)	1 (1.7)
Accidental Injury	1 (1.7)	4 (6.9)	2 (2.9)	4 (6.6)	3 (5.0)

[a] $p<0.001$

In an analysis of the cardiovascular effects of mixed amphetamine salts in this study, no statistically significant treatment-related effects were noted for the following parameters: systolic blood pressure, diastolic blood pressure, pulse rate, PR interval, QRS duration, QT interval, or QTcB interval. Investigators qualitatively assessed the incidence of clinically relevant change from baseline (Table 44. I). No patient experienced a systolic blood pressure ≥ 150 mmHg, diastolic blood pressure > 100 mm Hg, pulse ≥ 110 bpm, or QTcB interval ≥ 500 msec.[182,197]

Table 44. Incidence of clinically relevant change from baseline for cardiovascular parameters

Adverse Event n (%)	Mixed Amphetamine Salts				Placebo
	10 mg (n = 60)	20 mg (n = 58)	30 mg (n = 69)	40 mg (n = 61)	(n = 60)
Systolic Blood Pressure ≥ 20 mm Hg	2 (3.4)	2 (3.5)	4 (6.0)	3 (5.0)	1 (1.7)
Diastolic Blood Pressure ≥ 10 mm Hg	4 (6.9)	7 (12.3)	10 (14.9)	12 (20.0)	11 (18.3)
Pulse ≥ 25 bpm	0 (0.0)	2 (3.5)	2 (3.0)	1 (1.7)	0 (0.0)
QTcB interval ≥ 30 msec	5 (9.1)	3 (5.8)	3 (4.6)	2 (3.6)	3 (5.2)

Package Insert Data

Amphetamine-Dextroamphetamine

The safety information for amphetamine-dextroamphetamine was obtained from the package insert.[212] The extended release formulation was not assessed in this review. The available FDA review documents did not provide additional harms data in the pediatric population. The long-term effects of amphetamine-dextroamphetamine in the pediatric population have not been well assessed.[212]

Adverse events referenced in the warnings/precautions section of the package insert include: drug dependence, sudden death in patients with cardiac abnormalities, hypertension, heart rate increase, exacerbation of pre-existing psychotic disorder, mixed/manic episodes in patients with bipolar disorder, hallucinations, delusional thinking, mania, aggression, long-term suppression of growth, seizures, visual disturbances, exacerbation of tics and Tourette's syndrome, and impaired cognitive function.[212]

The additional adverse reactions reported in the prescribing information did not include a frequency.[212] These adverse events included: palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction, psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke, dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances, anorexia, weight loss, urticaria, rash, hypersensitivity reactions including angioedema and anaphylaxis, Stevens Johnson Syndrome, toxic epidermal necrolysis, impotence, changes in libido, and cardiomyopathy (associated with chronic use).[212]

Methylphenidate

The adverse event reports available for methylphenidate were gathered from the package insert.[213] The package insert utilized for this review included the immediate release and sustained release tablets.[213] FDA review documents for this product were not available for assessment.

Adverse events referenced in the warnings/precautions section of the package insert include: sudden death in children with cardiac abnormalities; hypertension; increased heart rate; aggravated symptoms of anxiety, tension, and agitation; mixed/manic episodes in patients with pre-existing bipolar disorder; hallucinations, delusional thinking, or mania; aggression; long-term suppression of growth; seizures; priapism; peripheral vasculopathy; Raynaud's Phenomenon; and visual disturbance.[213]

More frequent adverse events occurring in children taking methylphenidate included: loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia.[213] The exact frequency at which these adverse events occurred was not available.[213] Additional adverse events reported include: hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; angina; cardiac arrhythmia, libido changes, toxic psychosis, and Tourette's syndrome (rare).[213] Nervousness and insomnia were also reported but could be controlled by decreasing the dosage of methylphenidate and or not taking the medication in the afternoon or evening.[213] Adverse events reported but lack definite causal relationships include: abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; aggressive behavior; scalp hair loss.[213] Neuroleptic malignant syndrome (NMS) was also reported but occurred most often in patients taking other medications associated with NMS.[213]

Nonstimulants

Atomoxetine

Overview

Headache and anorexia were common side effects of treatment in the included studies. In the broader literature on atomoxetine (i.e. broader study populations,) the most common adverse events reported in clinical trials in child and adolescent patients (n = 1597) included: abdominal pain (18%), vomiting (11%), nausea (10%), fatigue (8%), irritability (6%), therapeutic response unexpected (2%), weight decreased (3%), decreased appetite (16%), anorexia (3%), headache (19%), somnolence (11%), dizziness (5%), and rash (2%).[214]

Systematic Reviews

We did not identify any systematic reviews addressing harms of atomoxetine.

Summary of Studies Reporting Harms Data

Two double blind, randomized clinical trials compared atomoxetine with placebo for management of oppositional defiant disorder.[176,179] In both studies, atomoxetine was titrated to a target dose of 1.2 mg/kg/day. One 9-week RCT,[176] considered poor quality for harms reporting, included 180 children between the ages of 6 and 17 years diagnosed with ADHD and either ODD (74.4%) or CD (24.4%) randomized to either fast or slow titrated atomoxetine or placebo. Table 45 summarizes treatment emergent harms. Rates of pre-defined clinically relevant adverse effects were higher in both treatment groups compared with placebo ($p<0.001$), but rates between treatment arms were not significantly different. One serious adverse event related to treatment (stomach cramps and abdominal pain) occurred in the fast titration arm. Eight participants in the active treatment groups (6 in the fast titration group, 2 in the slow titration group) discontinued the study due to adverse events: nausea and vomiting (n = 3), aggression (n = 1), fatigue (n = 1), headache (n = 1), tachycardia (n = 1), suicidal ideation of moderate severity (n = 1). Analyses of the effects of pretreatment use of psychostimulants and treatment emergent harms were not significant.

Another poor quality RCT enrolled children between the ages of 6 and 15 (mean: 9.9) years with ADHD and ODD symptoms.[179] Harms reported were generally considered mildly or moderately severe with five (undefined) instances of greater severity. Three children discontinued the study due to adverse events (reasons not defined). Body weight increased slightly in the placebo arm and decreased slightly in the atomoxetine arm ($p<0.001$) as did mean height ($p=0.021$). Table 45 outlines other harms reported.

Table 45. Harms reported in studies of atomoxetine

Author, Year Design (Quality)	Group [dose] (N at Final Analysis)	Treatment Group Reported Adverse Events, n (%)	Comparison Group Reported Adverse Events, n (%)
Dittman et al., 2011[176] RCT (Poor)	**G1:** Fast Titration atomoxetine [1.2 mg/kg/day] (44) **G2:** Slow Titration atomoxetine [1.2 mg/kg/day] (48) **G3:** Placebo [NA] (37)	**Fast Titration** Any Adverse Event: 70.0% Fatigue: 35.0% Headache: 25.0% Nausea: 21.7% Vomiting: 15.0% Abdominal Pain: 15.0% Anorexia: 15.0% **Slow Titration** Any Adverse Event: 57.4% Fatigue: 21.3% Headache: 14.8% Nausea: 19.7% Vomiting: 18.0% Abdominal Pain: 13.1% Anorexia: 11.5%	Any Adverse Event: 30.5% Fatigue: 10.2% Headache: 15.3% Nausea: 5.1% Vomiting: 5.1% Abdominal Pain: 0.0% Anorexia: 1.7%
Dell'Angelo 2009[179] RCT (Poor)	**G1:** Atomoxetine [1.2 mg/kg/day] (107) **G2:** Placebo [NA] (32)	Anorexia: 36 (33.6) Somnolence: 32 (29.9) Headache: 23 (21.5) Nausea: 22 (20.6) Abdominal Pain: 16 (15.0) Vomiting: 15 (14.0) Abdominal Pain, Upper: 11 (10.3) Decreased Appetite: 10 (9.3) Nervousness: 7 (6.5) Weight Decreased: 6 (5.6) Insomnia: 5 (4.7) Diarrhea: 4 (3.7)	Anorexia: 3 (9.4) Somnolence:2 (6.3) Headache: 4 (12.5) Nausea: 0 Abdominal Pain: 2 (6.3) Vomiting: 1 (3.1) Abdominal Pain, Upper: 4 (12.5) Decreased Appetite: 0 Nervousness: 2 (6.3) Weight Decreased: 1 (3.1) Insomnia: 2 (6.3) Diarrhea: 2 (6.3)

Package Insert Data

The adverse event data from the atomoxetine package insert were gathered from 5382 children or adolescent patients with ADHD participating in clinical trials in which 1625 were treated for longer than 1 year and 2529 were treated for over 6 months.[214] The original FDA review document contained extensive documentation of harms data.[215] A summary of this data is provided below.[215]

Adverse events referenced in the warnings/precautions section of the package insert include: suicidal ideation, severe liver injury, cardiovascular events (sudden death, stroke and myocardial infarction), increase in blood pressure and heart rate, orthostasis, syncope, emergent psychotic or manic symptoms, aggressive behavior, hostility, urinary hesitation, urinary retention, and priapism.[214]

The most common adverse events reported in clinical trials in atomoxetine receiving child and adolescent patients (n = 1597) included: abdominal pain (18%), vomiting (11%), nausea (10%), fatigue (8%), irritability (6%), therapeutic response unexpected (2%), weight decreased (3%), decreased appetite (16%), anorexia (3%), headache (19%), somnolence (11%), dizziness (5%), and rash (2%).[214]

Post-marketing reports specifically from adolescent patients revealed the following additional adverse events: paraesthesia, urinary hesitation, urinary retention.[214] Additional adverse events gathered from post-marketing data representing a combination of adults and

children included: QT prolongation, syncope, Raynaud's phenomenon, lethargy, hypoaesthesia, sensory disturbances, tics, depression and depressed mood, anxiety, libido changes, hyperhidrosis, male pelvic pain, and seizures.[214] It is important to note that in the patients that reported seizures, existing seizure disorders and additional risk factors for seizures may have been present.[214]

Infrequent serious adverse events reported in the sponsor's new drug application database included: seizure cases (n = 2), angioedema (n = 1), and elevated liver function test (n = 1).[215] An additional serious adverse event was reported in clinical trials: one patient with syncope.[215]

When compared to methylphenidate, the following adverse events occurred at least twice as frequent in the pediatric atomoxetine group (n = 313): vomiting (13.1%), asthenia (7.0%), allergic reaction (3.5%), sinusitis (3.5%), constipation (3.2%), hostility (3.2%), unexpected benefit (2.9%), abnormal dreams (2.6%), chest pain (2.6%), personality disorder (2.6%), gastrointestinal disorder (1.9%), sleep disorder (1.9%), nausea and vomiting (1.6%), gastroenteritis (1.3%), tooth disorder (1.3%), conjunctivitis (1%), ear disorder (1%), leukopenia (1%), mydriasis (1%), otitis externa (1%), and surgical procedure (1%).[215]

Guanfacine

Overview

In the one medium size study of guanfacine, somnolence, sedation, and headache were frequently reported treatment emergent adverse events.[177] We summarize additional potential adverse events reported in the FDA documentation.

Systematic Reviews

We did not identify any systematic reviews addressing harms of guanfacine.

Summary of Studies Reporting Harms Data

One 9-week, placebo-controlled RCT assessed extended release guanfacine (maximum dose 4 mg/day) in children between the ages of 6 and 12 years diagnosed with ADHD and ODD symptoms.[177] Use of concomitant ADHD medication was not allowed and was discontinued at the beginning of the study washout period. Treatment emergent adverse events occurred more frequently in the treatment group versus placebo (n = 114/136, 83.8% in the treatment arm vs. 45/78, 57.7% in placebo) and most were considered mild or moderate (Table 46). Predefined severe harms occurred in 14 children receiving guanfacine and in no children in the placebo group. Fourteen children in the treatment group (none in the placebo arm) also discontinued the study due to adverse events, which included sedation and somnolence. Baseline heart rate decreased by 11.6 beats per minute compared with 1.2 in the placebo arm. Twenty-five children in the guanfacine arm also developed abnormal heart rhythms during treatment. ECG analyses showed some changes from baseline in both groups but changes were not considered clinically significant. While the study noted contacting participants at 30 days post-treatment to assess for continuing harms, no longer term harms data are reported.

Table 46. Adverse events occurring in ≥5 percent of patients treated with guanfacine or placebo

Author, Year Design (Quality)	Group [Dose] (N at Final Analysis)	Harms in Treatment Group, N (%)	Harms in Comparison Group, N (%)
Connor 2010[177] RCT (Poor)	**G1:** Guanfacine Extended Release [1-4 mg/d] (136) **G2:** Placebo [NA] (70)	Any Treatment Emergent Adverse Event: 114 (83.8) Somnolence: 69 (50.7) Headache: 30 (22.1) Sedation: 18 (13.2) Upper Abdominal Pain: 16 (11.8) Fatigue: 15 (11.0) Irritability: 10 (7.4) Vomiting: 9 (6.6) Decreased Diastolic Blood Pressure: 8 (5.9) Dizziness: 7 (5.1) Heart Rate < 50 bpm: 7 (5.1) Nausea: 4 (2.9) Upper Respiratory Tract Infection: 4 (2.9) Pharyngolaryngeal Pain: 4 (2.9) Affect Lability: 2 (1.5) Sinus bradycardia: 24 (20.9)	Any Treatment Emergent Adverse Event: 45 (57.7) Somnolence: 4 (5.1) Headache: 14 (17.9) Sedation: 1 (1.3) Upper Abdominal Pain: 2 (2.6) Fatigue: 2 (2.6) Irritability: 4 (5.1) Vomiting: 5 (6.4) Decreased Diastolic Blood Pressure: 1 (1.3) Dizziness: 3 (3.8) Heart Rate < 50 bpm: 1 (1.3) Nausea: 4 (5.1) Upper Respiratory Tract Infection: 4 (5.1) Pharyngolaryngeal Pain: 4 (5.1) Affect Lability: 2 (2.6) Sinus bradycardia: 4 (6.8)

mg/d = milligram per day; RCT = randomized controlled trial; N = number; G = group; bpm = beats per minute

Package Insert Data

The safety and efficacy of guanfacine in pediatric patients has been reported in the medication package insert and the initial FDA approval documents.[216,217] Adverse events referenced in the warnings/precautions section of the package insert include: dose dependent decrease in blood pressure and heart rate as well as somnolence and sedation.[217] Adverse events for guanfacine can be separated by events occurring in patients receiving monotherapy or adjunctive therapy.

Common adverse events occurring in adult and pediatric patients taking guanfacine as monotherapy, at an incidence rate of more than 5 percent, and occurring at least twice as often as placebo included: somnolence, fatigue, nausea, lethargy, and hypotension.[217] Adverse events reported in short term clinical trials conducted in pediatric patients diagnosed with ADHD and taking guanfacine at fixed doses (incidence rate of more than 2%) included: somnolence/sedation, headache, fatigue, abdominal pain, dizziness, hypotension, dry mouth, nausea, lethargy, dizziness, irritability, decreased appetite, dry mouth, and constipation.[217]

Common adverse events occurring in the adult and pediatric patients taking guanfacine as adjunctive therapy, at an incidence rate of 5 percent or higher and occurring at least twice as often as placebo included: somnolence, fatigue, insomnia, dizziness, and abdominal pain.[217] Adverse events reported in short term clinical trials conducted in pediatric patients (age 6-17) diagnosed the ADHD and taking guanfacine at fixed doses (incidence $\geq$2%) included: headache, somnolence, insomnia, fatigue, abdominal pain, dizziness, decreased appetite, nausea, diarrhea, hypotension, affect lability, bradycardia, constipation and dry mouth.[217]

Adverse events reported in additional clinical trials included: atrioventricular block, sinus arrhythmia, dyspepsia, stomach discomfort, vomiting, asthenia, chest pain, hypersensitivity, increased alanine amino transferase, increased weight, convulsion, agitation, anxiety, depression, nightmare, increased urinary frequency, enuresis, asthma, hypertension, and pallor.[217] Additional common adverse event reported in the original FDA approval document for pediatric patients treated with guanfacine included: fatigue (14%), lethargy (6%), somnolence (30%), sedation

(10%), headache (23%), dizziness (6%), irritability (6%), insomnia (5%), affective lability (2%), nightmare (2%), upper abdominal pain (10%), nausea (6%), dyspepsia (3%), dry mouth (4%), constipation (3%), hypotension (6%), blood pressure decreased (2%), sunburn (2%), appetite decreased (5%). [216] In addition, 7 percent of patients taking guanfacine experienced hypotension compared to 3 percent of the placebo group.[217] Adverse events that were considered dose-related in patients taking guanfacine were hypotension, somnolence, sedation, abdominal pain, dizziness, dry mouth, decreased blood pressure, decreased heart rate, and constipation.[216] Based on these adverse events, it is not surprising that upon abrupt discontinuation of guanfacine, pediatric patients experienced transient rebound increases in blood pressure and heart rate.[216] Patients in the guanfacine group reported sedative effects more often than placebo (53% and 17% respectively).[216] These sedative effects included somnolence, sedation, hypersomnia, fatigue, lethargy, and asthenia.[216] Increased psychiatric related adverse events also occurred more often in guanfacine treated patients including: irritability (5%), affective lability (4%), aggression (1.4% vs. 0.7%), agitation (1.4%), depressed mood (0.8%), and anxiety (0.4%).[216]

In pediatric studies, patients discontinued guanfacine therapy due to (n = 513): hypotension (6), QT interval prolongation (3), bradycardia (1), somnolence (19), sedation (11), fatigue (8), asthenia (1), lethargy (1), dizziness (3), nightmare (1), insomnia (1), and headache (5).[216] Prolongation of the QT interval was considered a dose and exposure response relationship, i.e. greater exposure to guanfacine places patients at a greater risk of QT prolongation.[216] Specifically it was reported that the QTc interval would increase by 1 millisecond for every unit (ng/mL) increase in serum guanfacine.[216]

In long term studies (at least 12 months) guanfacine was found to increase patient's weight by an average of 17.2 pounds.[216] Serious adverse events in these long-term studies included (n = 446): syncope (7), loss of consciousness possibly due to a syncopal episode (1), orthostatic hypotension (1), seizures (2), accidental medication overdoses (2) and intentional medication overdose (1).[216] According to the literature, the rate of syncope in pediatric populations requiring medical attention have been estimated at 126 to 300 per 100,000 per year.[216]

Post-marketing studies reported that in 21,718 patients taking guanfacine 1 mg/day for 28 days experienced the following adverse events (more than 1% incidence): dry mouth, dizziness, somnolence, fatigue, headache, and nausea.[217] Additional adverse events reported less frequently include: edema, malaise, tremor, palpitations, tachycardia, paresthesias, vertigo, blurred vision, arthralgia, leg cramps, leg pain, myalgia, confusion, hallucinations, impotence, dyspnea, alopecia, dermatitis, exfoliative dermatitis, pruritus, rash, and alterations in taste. [217] In addition, syncope was reported in 10 guanfacine treated pediatric patients; which occurred after long exposure to the medication.[217] The sponsor provided additional post-marketing data by searching FDA's adverse drug reactions (ADRs) and adverse event reporting system (AERS) for guanfacine related adverse events reported between January 1, 1969 to March 31, 2005.[216] This search uncovered 955 adverse events reported for 309 pediatric patients (age <17).[216] The most commonly reported adverse events included: somnolence (22 events), drug ineffective (19), aggression (18), fatigue (15), weight increased (15), abnormal behavior (12), tic (12), nausea (11), anger (10), disturbance in attention (10), mania (10), sedation (10), agitation (9), condition aggravated (9), insomnia (9), lethargy (9), vomiting (9), and weight decreased (9). [216] Serious adverse events identified included: death (3), convulsion (18), loss of consciousness (7), depressed level of consciousness (4), stupor (3), cardiac arrest (2), cardiac failure (2), myocardial infarction (2), syncope (3), chest pain (4), aggression (18), abnormal behavior (12), tic (12),

attention disturbance (10), mania (10), agitation (9), hostility (8), irritability (7), mood swings (7), psychomotor hyperactivity (7), and movement disorder (3).[216]

Studies assessing adverse events in children (ages 6-17) with ADHD receiving guanfacine (4 mg/day) in combination with a stimulant medication revealed the following psychiatric adverse events: irritability, anxiety, insomnia, initial insomnia, depression.[216] Common adverse events reported in these patients included: fatigue (35%), headache (33%), upper abdominal pain (32%), irritability (23%), somnolence (19%), and insomnia (16%).[216]

Key Question 6: Do interventions intended to address disruptive behaviors and identified in Key Questions 1-4 vary in effectiveness based on patient characteristics (KQ6a), characteristics of the disorder (KQ6b), treatment history of the patient (KQ6c), or characteristics of the treatment (KQ6d)?

Overview of the Literature for KQ6

We identified 24 studies[88,89,98,100-102,104,106,119,120,122,125,126,129,130,134-136,138,140,179,182,187,218] reported in 37 publications[88,89,98,100-102,104,106,119,120,122,125,126,129,130,134-136,138,140,156,159,162,163,166,169-172,179,182,187,218-222] that addressed KQ6.

Patient Characteristics (KQ6a)

Psychosocial Interventions

Five studies of preschoolers reported tests for mediation and moderation by patient characteristics. Three of those were in studies of the Incredible Years program, and results were inconsistent.[138,158,159] One publication[158] reported that single parenthood, low socioeconomic status, and teen parenthood, did not significantly moderate change in ECBI scores over the course of treatment with IY. However, sex, age, and maternal depression were significant moderators with boys in the IY groups having better outcomes compared with girls (effect size: 0.03, p=0.04). Younger children also had better conduct problem outcomes compared with older (effect size: 0.03, p=0.04), and children of depressed mothers in the IY group had improved outcomes compared with children of depressed mothers in the control group (effect size: 0.05, p=0.004). By contrast, a study of the IY parenting intervention,[138] also examined the impact of patient characteristics such as child age, sex, risk of poverty, disadvantaged socioeconomic status, and risk factors for conduct disorder (single parent, teenage parent, parental depression, family poverty, parental drug use or criminal history) and did not report similarly significant moderation effects for ECBI outcomes. A third study[102] reported that child gender and maternal education were significant effect moderators.[159]

One study of Triple P in preschoolers tested for mediation and moderation and did not report that any of the examined variables (family risk factors, baseline maternal rated ECBI Intensity) predicted treatment outcome.[140,160,162] The study of PCIT in preschoolers testing for mediation by patient characteristics reported that baseline respiratory sinus arrhythmia moderated treatment outcomes.[98,156]

Four studies of psychosocial interventions for disruptive behaviors in school-age children reported tests for mediation and moderation.

Two studies reported no mediation or moderation of treatment effects for gender[134] and child welfare system involvement;[89] one study reported significant moderation by neighborhood[223] and

another reported that in a test nine potential moderator variables on three outcome variables that children of younger mothers appear to have benefitted more but also that this finding could likely just have been by chance given the number of comparisons.[122] Finally, one study of the Project Support intervention reports partial mediation of CBCL and ECBI over time within individuals was present for several variables examining characteristics of children's mothers including inconsistency, mother-child psychological aggression, and mother's trauma history. Maternal Global psychiatric symptoms also demonstrated partial mediation and were more strongly related to child outcomes in the Project Support group than in the comparison group.[100]

Three studies tested for potential mediation and moderation among the group of studies evaluating psychosocial interventions for teenagers with disruptive behaviors.

Two studies indicated potential moderation of treatment effects by family functioning-related variables.[106 172] For example, one secondary analysis of data from an RCT comparing MST to treatment as usual reported that families with more adaptive functioning at baseline benefitted more from MST.[172] One study reported that MST had greater positive effect among boys than among girls.[136]

Taken together, there is some evidence that treatment outcomes may vary based on patient characteristics, but results are inconsistent likely due to heterogeneity across individual studies.

Pharmacologic Interventions

No identified studies addressed KQ6a.

Characteristics of the Disorder (KQ6b)

Psychosocial Interventions

Inconsistent results are reported for the potential mediating and moderating impact of baseline severity of child disruptive behaviors for treatment outcomes.[102,129,158,159] Personality traits such as difficult temperament in preschoolers[102,159] and psychopathy in teenagers[120,169] were identified as potential mediators or moderators. The one study that examined the impact of concomitant developmental disabilities in a small subsample of the overall study sample was shown to weaken effectiveness of one intervention in school-age children.[88]

For studies of preschoolers, post-hoc mediator and moderator analyses in one RCT (reported in 2 publications)[129,158] of IY compared with a waitlist control group tested the effects of multiple variables on outcomes and reported that baseline child deviant behaviors did not significantly moderate ECBI scores. Another RCT (also reported in 2 publications)[102,159] compared a nurse-led IY intervention, psychologist-led IY, and delivery of the IY book without specific therapist-led intervention to parents assessed multiple potential predictors, mediators, and moderators of outcomes on the CBCL and ECBI. Higher baseline levels of life stress, parent stress, child behavior problems, and parent-child dysfunction were associated with greater improvement on the ECBI Intensity scale and CBCL Externalizing scale, but lower levels of life stress, difficult child temperament, and parent-child dysfunction were associated with greater treatment gains on both measures ($p<0.01$).

Regarding potential mediation and moderation of treatment effects for school-age children with disruptive behaviors, one study showed that one intervention (PPCP) was more effective for children with behavioral problems (but no developmental delay) than for children with behavioral problems plus developmental delay.[88] One publication[220] from an RCT[101] of school-aged children referred for disruptive behavior and randomized to receive the intervention

described above as Modular in a community or outpatient clinic setting examined associations between characteristics of the primary or comorbid disorders at baseline and end of treatment outcomes. Baseline CD was a strong predictor of persistent CD symptoms over time. This suggests that baseline CD is associated with reduced effectiveness, at least for the intervention examined in this study. Similarly, this study looked at specific ODD symptoms and reported that the ODD hurtful dimension, which is described as spiteful or vindictive behaviors, was also associated with reduced intervention effectiveness.

Studies examining potential mediation and moderation of treatment effect that examined interventions for teenagers with disruptive behaviors reported that psychopathy and family characteristics partially mediated / moderated treatment effect. In one study of MST, MST was found to be more effective in decreasing externalizing problems for youth with less psychopathy (defined as callous/unemotional traits, narcissism, and impulsiveness).[169] Another study of MST similarly reported that youth scoring lower on a measure of callous/unemotional traits and narcissism benefitted more from MST than did youth scoring higher on each of these measures.[120]

Pharmacologic Interventions

Comorbid ODD is commonly present in children and adolescents with ADHD, and studies frequently included participants with both. In the two RCTs of atomoxetine and one RCT of guanfacine, inclusion criteria specified children with ODD *and* comorbid ADHD a priori, based on strict diagnostic criteria.[176,177,179,190] For the two RCTs of stimulants; the population included a large proportion (nearly two thirds) of patients with comorbid ADHD[182,187] but because results are not provided for participants with and without ADHD, the added or separate effect of ADHD on effectiveness of the treatment cannot be discerned.

Severity of disease at baseline may be an important mediator in treatment response. Baseline SNAP-IV ODD scores ranged from 15.5 (4.4) in one RCT of atomoxetine[176] to 17.2 (3.3) in a second RCT of atomoxetine.[179] All three RCTs of nonstimulants found significant effects regardless of baseline symptom levels.

One RCT of the stimulant mixed amphetamine salts extended release[182] looked at the treatment effect stratified by baseline severity (based on baseline ODD subscale score $\geq$1.7) in a post hoc reanalysis of the per protocol population. The mean change from baseline in ODD scores on the SNAP-IV ODD parent rating was greater for the high baseline ODD severity group. Of note, the baseline scores were low in almost half of the population of the study.

It is not clear if treatment-related changes in ODD symptoms are independent of changes in ADHD symptoms in this population. One study of atomoxetine[176] used a path analysis to evaluate if the treatment effect on ODD symptoms were influenced through the treatment effect on ADHD and/or CD symptoms; they found a nonadditive effect, implying a negative direct effect of atomoxetine on ODD symptoms. In a post hoc analysis of another atomoxetine RCT, authors found that the percent reduction from baseline to endpoint in oppositional symptoms (CPRS-R:L ODD subscale) and ADHD symptoms were highly correlated (r=0.74).

Treatment History (KQ6c)

Psychosocial Interventions

No identified studies addressed KQ6c.

Pharmacologic Interventions

Only one RCT of atomoxetine[176] examined the interaction of treatment history defined as prior treatment with a stimulant on study outcomes. Overall, 44 percent of participants had received prior treatment with stimulant medication. In a post hoc analysis, there was a significant interaction (p=0.032) between prior stimulant treatment status and study outcome. Both groups improved over the course of treatment with atomoxetine, but the effect of treatment was greater among the patients with a prior history of stimulant treatment (effect size: 0.860) than for the non-pretreated patients (effect size: 0.165). Replication of this finding in other studies is needed.

Characteristics of the Treatment (KQ6d)

Psychosocial Interventions

Studies of psychosocial interventions for children with disruptive behaviors examining if interventions varied in effectiveness based on characteristics of the treatment primarily evaluated variation based on dose and, for interventions including a parent component either alone or in combination with other components, based on whether changing parenting practices mediated intervention effectiveness.

Four studies examined the potentially moderating impact of dose and reported inconsistent effects.[102,104,122,126] One RCT conducted in Norway examined the dose-response relationship by comparing intervention effectiveness for mothers attending at least 75 percent of the scheduled sessions to those who did not and reported more improvement on parent reported outcomes of child disruptive behaviors for mothers who attended more than 75 percent of sessions than those who attend less sessions.[126] One RCT conducted in Sweden reported complete mediation of the effect of parent management training on child disruptive behaviors for dose as defined by a measure of the extent to which parents had completed assigned homework.[122] One RCT conducted in the United States examined the impact of a cognitive behavioral group therapy for adolescents with depression on comorbid disruptive behaviors, as compared to life skills tutoring. The authors evaluated the impact of dose as defined by group attendance.[104] The interaction of group attendance by treatment arm was nonsignificant. One RCT conducted in the United States examined the impact of IY programs led by primary care nurses (group 1) or psychologists (group 2), in comparison to giving parents the IY book but no specific interventionist-led training.[102,159] Dose effect analyses suggest that the children of parents who attended more training sessions showed more improvement.[159]

Eleven studies examined whether the effectiveness of interventions delivering a parent component, alone or in combination with other intervention components, was mediated by changes in parenting practices, confidence, or stress.[87,119,120,122,125,129,130,146,158,170,219]

Three studies of preschool-age children examined this potential mediator. One prospective cohort study evaluating IY parent training compared with usual care reported that improvement in child conduct problems was mediated by decreased parental use of critical statements.[87] One RCT comparing IY to a waitlist control group tested the effects of multiple variables on outcomes,[129,158] and reported that intervention status correlated with improvement in positive but (not negative) parenting behavior, which in turn was itself correlated with improvements on the ECBI (p<0.014). An RCT evaluated an intervention program (Hitkashrut) combining elements of parent training models including parental self-regulation, involvement of fathers, parent-child communication skills, and behavior management compared with undefined minimal

intervention.[119] Intervention group changes in child conduct problems from baseline to post-treatment were mediated by changes in parenting practices and parent reported stress.[119]

Four studies of school-age children examined this potential mediator. One study reported that improved positive parenting skills and that reduced harsh and inconsistent parenting partially mediated intervention effectiveness.[122] One study reported that reduced harsh and inconsistent parenting skills partially mediated intervention effectiveness, but that improvements in positive parenting skills did not.[219] Two studies reported that improved positive parenting skills partially mediated parent reported child disruptive behaviors.[125,130,166]

Pharmacologic Interventions

No identified studies addressed KQ6d.

Discussion

State of the Literature

KQ1. Effectiveness of Psychosocial Interventions

Sixty-six studies examined the effectiveness of psychosocial interventions for children with disruptive behaviors. We categorized these studies broadly by age group as examining preschool (n = 23), school-age (n = 29), or teenage (n = 14) children, and according to whether the active treatment arm was an intervention that included only a child component (n = 2), only a parent component (n = 25), or was a multicomponent intervention (n = 39). Multicomponent interventions were defined as those that included two or more of a child component, parent component, or other component (e.g., teacher component, family together component). Studies within each of these intervention categories were heterogeneous, although several well-known programs were most common.

We included studies of interventions delivered in healthcare settings for children with a formal diagnosis of a disruptive behavior disorder or whose disruptive behaviors were assessed at or above a clinical cutoff on a well-validated measure of child disruptive behaviors. Thus, we excluded from our review studies of preventive or universal interventions, and interventions delivered in non-healthcare settings. These important interventions and populations may be appropriate for a separate review, but were beyond the scope of our review. We also excluded disruptive behaviors in the context of autism or other developmental disabilities. We included studies of children who had conditions such as attention deficit hyperactivity disorder (ADHD) as long as the primary focus of the study was on the treatment of the disruptive behavior. We also focused on parent reports of child disruptive behaviors because they were the most consistently reported outcome in the literature, because other outcomes of interest, especially functional outcomes such as school performance, were not consistently reported.

Preschool Children

Studies examining psychosocial interventions for preschool-age children had an active treatment arm that included only a parent component (n = 14) or were multicomponent interventions (n = 9). Seventeen of the 23 studies included in our review of psychosocial interventions for preschoolers with disruptive behaviors examined one of three interventions: Parent Child Interaction Therapy (PCIT) (n = 7), the Incredible Years Parent Training program (IY-PT) (n = 5), or the Positive Parenting Program (Triple P) (n = 5). The remaining six studies each examined a different intervention.

The seven studies examining PCIT for preschool disruptive behaviors evaluated several versions of PCIT (regular, abbreviated, culturally adapted) in comparison to treatment as usual, a waitlist control group, or another PCIT version. Although most studies measured child disruptive behaviors using the Eyberg Child Behavior Inventory (ECBI) Intensity and/or Problem subscales, most studies included other measures of child disruptive behaviors (e.g., Dyadic Parent-Child Interaction Coding System) and did not clearly identify one outcome measure as primary. All five of these studies reported significant reductions in parent-reported child disruptive behaviors from baseline to post-treatment in comparison to either treatment as usual or a waitlist control group, regardless of which version of PCIT was being evaluated. Consistent differences between versions of PCIT were not reported.

The five studies examining IY-PT for preschool disruptive behaviors evaluated several versions of IY-PT (IY-PT + ADVANCE, IY-PT, IY-PT psychologist led, IY-PT nurse led) in comparison to other versions of IY-PT and waitlist controls. All studies used one of the parent-reported ECBI scales or CBCL scales, and most of the studies included direct observation of child disruptive behaviors. On parent-reported measures of child disruptive behaviors, 5 studies reported improvement from baseline to followup (ranging from post-treatment to 2-year followup) for children in IY-PT. Children in the IY-PT arms consistently showed more improvement than children in waitlist control arms. Consistent differences between versions of IY-PT were not reported.

The five studies examining Triple P for preschool disruptive behaviors evaluated several different versions of Triple P against each other, a waitlist control group, and treatment as usual. Each of these studies reported significant reductions in disruptive behaviors in the Triple P treatment arm as compared to a waitlist control group on parent-reported child disruptive behaviors as measured by one of the ECBI subscales. Self-directed Triple P plus weekly phone conferences was found to be more effective than self-directed Triple P alone,[135] and self-directed Triple P plus 14 hours of skills training and partner support was more effective than self-directed Triple P plus 10 hours of therapist-led skills training or self-directed Triple P alone.[140]

Although six other studies also examined interventions for preschoolers with disruptive behaviors, each examined a different individual intervention making it difficult to make general statements about these interventions.

Overall, most of the reviewed studies on psychosocial interventions for preschool children with disruptive behaviors focused on one of three specific interventions (PCIT, IY-PT, or Triple P). The literature for this age group is limited by difficulties defining the study population, study design limitations even among the RCTs, and lack of consensus about the most important outcomes.

School-Age Children

Seventeen of the 29 studies included in our review of psychosocial interventions for school-age children with disruptive behaviors had an active treatment arm that was a multicomponent intervention. Eleven studies included only a parent component and one study included only a child component. Four of the 15 studies of multicomponent interventions included at least two of the IY components (child training, parent training, and teacher training) in combination with one another, two were of a modular intervention, and two were of SNAP Under 12. The seven remaining studies were each of a different intervention.

Four studies examined more than one IY component in combination with each other. Because these studies test multiple IY component combinations against each other and waitlist control and measure multiple outcomes without designating a primary outcome, this group of studies is difficult to summarize succinctly. A conservative summary is that at least two IY components delivered together are associated with greater decreases in parent-reported child disruptive behavior than waitlist control.

Two studies (each including multiple papers) examined the effects of a community-based version (in comparison to a clinic-based version) or nurse-led version (in comparison to enhanced usual care) of a modular multicomponent intervention for children with ODD or CD. Both studies were therefore essentially testing the "portability" of this intervention. Although the nurse-led version was associated with improvement in goal achievement and overall health, it was not associated with significantly more improvement in parent-reported child disruptive

behaviors than was enhanced usual care. Both the clinic- and community-based versions of the intervention were associated with significant reductions in parent-report child disruptive behaviors.

Two studies (one RCT, one non-RCT) compared the SNAP Under 12 intervention in comparison to a waitlist control group that engaged in recreational group activities. Children in SNAP Under 12 group in both studies showed greater reductions over treatment in parent-reported child disruptive behaviors as measured by the CBCL Aggression and CBCL Delinquency subscales. Only one study has been published for each of the remaining seven multicomponent interventions.

Of the 11 studies examining parent only interventions, three studies examined IY-PT, two studies examined PMTO, and six other studies each examined a different intervention with only a parent component. Two studies examined IY-PT in comparison to a waitlist control group. Each study reported significantly greater reductions on ECBI-I, ECBI-P, or both for children in IY-PT groups compared with the children in the control groups. Both of the studies examining PMTO reported that children receiving PMTO showed greater reductions in parent-reported child disruptive behaviors relative to treatment as usual. It is difficult to make general statements about the other six studies because they are each of a different intervention.

There was only one study including interventions with only a child component for school-age children. The study examined a social cognitive intervention program.[132] As with the literature examining psychosocial interventions for preschool-age children, the literature on school-age children suggests that there is most support for multicomponent interventions that include a parent component. Overall limitations for the school-age literature are similar to that for preschoolers and are discussed in detail below.

Teenage Children

Thirteen of the 14 included studies examining psychosocial interventions for teenagers with disruptive behaviors had an active treatment arm that was a multicomponent intervention, specifically MST (n = 5) or BSFT (n = 3). The other three studies were each of a different intervention.

All five of the studies examining MST were RCTs. Two of these studies were conducted in the United States: one compared MST to treatment as usual;[94] the other compared MST to individual therapy.[111] Both of these studies demonstrated greater reductions in child disruptive behaviors for children receiving MST. The other three studies were conducted in Europe and compared MST to treatment as usual.[120,124,136] One RCT compared youth randomized to receive MST with youth randomized to receive a treatment as usual intervention that was much more comprehensive than the type of treatment as usual most commonly included in studies conducted in the United States.[120] This RCT reported that in comparison to youth randomized to the treatment as usual multicomponent intervention youth randomized to MST were less likely to have committed nonviolent offenses and experienced greater reductions in the CBCL Aggression and Delinquency subscales, but did not experience greater reductions in the CBCL Externalizing subscale from baseline to the end of followup.[120] One RCT compared MST to treatment as usual reporting that youth randomized to receive MST experienced greater decreases in disruptive behaviors as measured by the CBCL Externalizing subscale, ODD and CD as measured by a *DSM-IV* symptoms checklist, and property offenses than did youth randomized to receive treatment as usual.[136] The final of the RCTs conducted outside the United States compared MST to treatment as usual and reported no difference in disruptive behaviors as

measured by the CBCL Externalizing subscale for youth randomized to receive MST as compared to youth randomized to receive treatment as usual.[124]

Three RCTs examined BSFT in comparison to group therapy[106] or another family-based intervention.[142,144] Although each of these studies examined the effectiveness of BSFT with a very specific subgroup (Hispanic teenagers)[106] or very specific outcome (bullying),[142,144] all three reported significant reductions in child behavior problems for the youth randomized to receive BSFT in comparison to group therapy[106] or another multicomponent intervention.[142,144]

Although it is difficult to make general statements about each of the other four interventions included in this review because there is only one study of each, taken together the literature on psychosocial interventions for teenagers with disruptive behaviors suggests most support for multicomponent interventions such as MST or BSFT. Overall limitations are similar for teenage literature as for the two other age groups and are discussed in detail below.

Summary of Meta-Analysis

We conducted a Bayesian multivariate, mixed treatment (network) meta-analysis using data from RCTs addressing KQ1 that measured parent-reported child disruptive behavior using one of the most prevalent outcome measures (i.e., CBCL Externalizing subscale reported as a T-score, ECBI Intensity subscale, or ECBI Problem subscale) and included the necessary data at baseline and post-treatment for both intervention and control groups. In total, 28 studies were used to fit the model. The baseline was subtracted from the end-of-treatment mean and used as the response measure, along with the sum of their standard deviations. Our outcome variable was a standardized mean effect size. Our predictor variable was the broad category of intervention (child component only, parent component only, multicomponent) with the specific intervention type (PCIT, MST, etc.) defined as a random effect.

The effect sizes for the multicomponent intervention class and for interventions with only a parent component had the largest estimated value (Table 47), both with a median of −1.2 (95% credible interval: −1.6 to −0.9) standard deviations reduction in outcome score. The estimate for interventions with only a child component was −0.9 (95% Credible Interval: −1.6 to −0.4). Accordingly, multicomponent component interventions and interventions with only a parent component had the highest probability of being the best intervention (43% for both), followed by interventions with only a child component (14%).

Table 47. Network meta-analysis of intervention category as a predictor of treatment effect in parent-reported measures of child disruptive behavior among selected studies of psychosocial interventions

Intervention Class	Posterior Median	Standard Error	95% Credible Interval
Child-only	−0.9	0.3	[−1.6, -0.4]
Parent-only	−1.2	0.2	[−1.6, −0.9]
Multicomponent	−1.2	0.2	[−1.6, −0.9]

Age effects were relatively more subtle, with an additive median effect of −0.4 standard deviations (95% credible interval: −0.6 to −0.3) for preschool relative to school-age children (baseline level), and of −0.1 standard deviations (95% credible interval: −0.5 to 0.2) for adolescents relative to school-age children. These trends were evident across each of the outcome measures included in the analysis.

The marginal posterior probabilities of remaining above the cut point were higher for the treatment as usual/control group relative to each intervention group, with multicomponent interventions showing the lowest proportion of children still above the clinical cutoff post-treatment.

Though we considered age-by-treatment interactions, there was not enough balance among the age and treatment combinations to include them in the final model.

Overall Summary of KQ1

Our qualitative and quantitative syntheses generally suggest that available evidence provides the most support for interventions for children with disruptive behaviors that are multicomponent interventions or interventions that include only a parent component. All multicomponent interventions included in this study included a parent component. Our assessment of the overall strength of evidence and limitations of this evidence base are discussed in detail below and in an Evidence Profile (Appendix J). Overall, the evidence base is limited by difficulty defining the study population, study design limitations even among RCTs, and lack of consensus about the most important outcomes.

KQ2. Effectiveness of Pharmacologic Interventions

Despite a fairly robust literature on psychopharmacologic drugs as a whole, few studies have focused specifically on their use in children whose primary indication is a disruptive behavior disorder. Among those studied are four types of drug treatment: antipsychotics, antiepileptics, stimulants typically used with ADHD, and nonstimulants typically used with ADHD. Thirteen studies were identified across all of these drug classes, with the most commonly studied drug being risperidone. All studies were conducted in primarily male patient populations, with ages ranging from 6 to 18 years.

Four antipsychotics were studied: risperidone, quetiapine, aripiprazole, and ziprasidone. All of the antipsychotics are second-generation atypical antipsychotics. Prior systematic reviews have studied these drugs and others for a more general set of indications. We describe the findings of those reviews in below in order to place our more limited review in context. Four antipsychotics were studied: risperidone, quetiapine, aripiprazole, and ziprasidone. All of the antipsychotics are second generation, atypical antipsychotics. There is a large literature base as well as prior systematic reviews that have studied these drugs and others for a more general set of indications and are available.

Among antipsychotics, risperidone was assessed in three studies and the others were each in only one study. Among studies of risperidone, two studied the effectiveness of risperidone as the initial treatment, and one focused on maintenance, comparing continued use of risperidone to discontinuation and replacement with placebo. One study[186] reported a positive effect of risperidone over placebo. The second study[181] compared risperidone as augmentation to stimulant medication for patients with ADHD and aggressive behavior after treatment with a stimulant and found no benefit of risperidone over placebo. The final study[183] was a maintenance study, comparing risperidone to placebo after treatment with risperidone. In this study, the placebo group worsened more than the risperidone group over 6 months.

One open label study[224] compared aripiprazole to ziprasidone and found the two medications to be equally effective in decreasing clinically significant aggressive behavior over two months.

Finally, one study compared the use of quetiapine to placebo and the results were mixed. Although clinicians rated greater improvement in symptoms in the quetiapine group, there was

no difference on parent rated measures, and no difference in CPRS (a rating of general problem behaviors in children). Quality of life was reported to be significantly higher in the treatment group, however.

Overall, these studies were limited by short duration (all but one[183] were 2 months or less) or high attrition. While head-to-head studies such as that comparing aripiprazole to ziprasidone are useful to compare medications, large, randomized, controlled studies that measure effect size and show consistent benefit of this class of medications over placebo are also needed.

Among antiepileptic drugs, only valproic acid was studied specifically for disruptive behavior disorders. The one placebo-controlled trial[178] reported no benefit for valproic acid, while a small (n = 20) crossover study of slightly older (up to age 18) children reported a benefit for drug. Finally, one study provided valproate to all participants, but compared high and low doses, with greater effects reported for higher doses and in "high distress" conduct disorder relative to "low distress" conduct disorder. All three studies were small, short-term and funded by the manufacturer of the treatment drug.

Medications commonly used for ADHD, both stimulants and nonstimulants, have also been studied for their potentially specifically to manage disruptive behaviors among children with comorbid ADHD and ODD/CD. Among the nonstimulants, Atomoxetine, a centrally acting, norepinephrine reuptake inhibitor, has been approved for treatment of ADHD in children and adolescents and has been used off label for treatment of DBD and ODD symptoms among populations with comorbid ADHD.

Two RCTs[176,179] reported treatment with atomoxetine (up to 1.2 mg/kg/day) for nine weeks improved ODD symptom scores compared to placebo, among children and adolescents with ADHD and comorbid ODD. One RCT (reported in 2 publications)[176,190] reported significant improvement in quality of life compared to placebo, over the 9-week period. The other RCT[179] found no significant differences in overall quality of life, but improvement in certain subdomains, including risk avoidance and emotional comfort.

Guanfacine extended release is a selective central alpha2A-adrenergic receptor agonist and is FDA approved for treatment of ADHD in children 6 to 17 years. We identified one low risk of bias RCT of guanfacine extended release (1 to 4 mg/day) that reported significantly reduced oppositional symptoms as measured by the CPRS-R:L oppositional subscale scores compared with placebo.

Although there were a limited number of studies, these three RCTs reported short-term effectiveness in reducing ODD/CD symptoms among children and adolescents with comorbid ADHD and ODD.

One high risk of bias RCT of mixed amphetamine salts extended release demonstrated that higher doses (30 mg/day) were associated with decreased ODD symptoms compared to placebo over a 4-week period among school-aged population with ODD, 79 percent of who also met criteria for ADHD. This study also reported significant improvement in several quality of life measures for children with ODD. One high risk of bias RCT of methylphenidate (up to 60 mg/day in 2 divided doses) among school-aged population with CD symptoms, 69 percent of who also met ADHD criteria, found both teacher and parent ratings of CD problems improved compared to those in the placebo group. Duration of these two studies was short, ranging from 4-5 weeks, which is too short to determine whether there is a long-term treatment effect of stimulants on ODD symptoms. Severity of ODD symptoms at baseline may be important mediator in treatment response, but more data are needed to examine this question.

Overall, studies are lacking that compare children/adolescents with ADHD alone to those with ADHD with ODD and ODD alone in order to evaluate the specific effects of treatment on oppositional symptoms. Comorbid ODD is commonly present in children and adolescents with ADHD, and thus finding populations with ADHD but without ODD symptoms or ODD without ADHD may be challenging. Most importantly, it is unclear whether treatment-related changes in ODD symptoms are independent of changes in ADHD symptoms in this population. Treatment period of 8 to 9 weeks may be too short to determine whether there is a long-term atomoxetine treatment effect on ODD symptoms or quality of life outcomes.

Although combination therapy with antipsychotics and stimulants can be effective for patients with ADHD and comorbid DBD, we found a lack of studies that evaluated combination pharmacologic treatment compared to monotherapy or compared the efficacy of combined behavioral and pharmacologic interventions compared to pharmacologic or behavioral interventions alone. To date, treatment research is almost exclusively supported by the pharmaceutical industry. Given the prevalence of DBDs and the need for high quality data to inform clinical practice, more long-term studies are needed.

KQ3. Effectiveness of Psychosocial Versus Pharmacologic Interventions

No head-to-head studies were found to answer this question.

KQ4. Effectiveness of Combined Psychosocial and Pharmacologic Interventions

No head-to-head studies were found to answer this question.

KQ5. Harms of Psychosocial or Pharmacologic Interventions

No harms of psychosocial interventions were reported. Importantly, a lack of reported harms is not an indication that no harms exist. The psychosocial literature also uniformly failed to note that harms were sought.

The medical treatment studies in this report were generally small and short term, with typically no followup post treatment. Thus, harms reported in those studies were generally mild or moderate and fairly immediate in nature. Nonetheless, there was significant loss to follow up in several studies, some of which was clearly due to experiencing adverse events and the studies were very short term and not powered to identify harms that might be rare. All of the pharmacologic studies included in the empirical literature here were designed and powered for benefit and thus would only be likely to identify common and minor events. Therefore, we sought harms data from other sources that might include more extensive and longer-term data, including other systematic reviews. It is important to note that other studies, including large scale, database analyses have identified harms of antipsychotics in particular to include significantly increased risk of metabolic effects.

Harms of the antiepileptic drug, valproate, were available from three, short-term RCTs. They include short-term changes in sleep pattern, mood changes, gastrointestinal upset and appetite changes. The proportion of patients experiencing these were high some cases (e.g. 50% with insomnia in the treated group versus 15% in placebo), but the numbers of participants included were so low as to likely be unstable. Additional data are available from FDA package inserts and provide more support for these adverse events. Specifically in pediatric clinical trials, consisting

of 76 patients aged 10 to 17 years taking divalproex extended release for mania and 231 patients aged 12 to 17 years taking divalproex extended release for migraine, common adverse events (reported more than 5% and twice the rate of placebo) included: nausea, upper abdominal pain, somnolence, increased ammonia, gastritis and rash.[211]

Harms of antipsychotics have been studied extensively, both in the context of effectiveness research and independently, and are reviewed in other systematic reviews. The systematic review data mirror that available in our included studies, namely identifying significant increases in somnolence, fatigue and weight gain.[183]

We identified three good quality systematic reviews addressing harms of atypical antipsychotics in children and adolescents.[49,52,198] Harms found to be significantly associated with treatment included weight gain and changes in metabolic parameters.[49] Mean weight gain in the risperidone group was 2.37 kg more than in the placebo arm over 6 to 10 weeks in a meta-analysis of two trials (mean difference: 2.37, 95% CI: 0.26 to 4.49).

Another Agency for Healthcare Research and Quality (AHRQ) review included studies of atypical antipsychotics used for any indication in individuals aged 24 years and younger.[52] Agents included in studies in the review were haloperidol, risperidone, aripiprazole, olanzapine, pimozide, quetiapine, clozapine, and ziprasidone, and median study duration was 8 weeks. The review evaluated harms by drug class and noted fewer extrapyramidal symptoms associated with olanzapine and risperidone compared with haloperidol (low strength of the evidence), and no significant differences between first and second-generation antipsychotics in prolactin-related adverse events (low strength of the evidence). Risperidone was associated with less dyslipidemia and less weight gain that olanzapine (moderate strength of the evidence). Risperidone was also associated with more prolactin-related harms than olanzapine (moderate strength of the evidence) and with more weight gain than aripiprazole (low strength of the evidence).

Finally, one review and meta-analysis evaluated metabolic and neurologic adverse events associated with second-generation antipsychotic use in children with any mental health disorder and included 35 RCTs (4 reported in the current review).[198] In a meta-analysis of 10 RCTs of risperidone of less than 12 weeks duration, weight gain (mean difference: 1.72 kg, 95% CI: 1.17 to 2.26, $p<0.00001$), prolactin levels (mean difference: 20.70 ng/mL, 95% CI: 16.78 to 24.62, $p<0.00001$), and change in prolactin from baseline to end of treatment (mean difference: 44.57 ng/mL, 95% CI: 32.24 to 56.90, $p<0.00001$) were higher in risperidone groups compared with placebo. The odds of clinically significant weight gain were higher in the risperidone arm compared with placebo (OR=2.90, p=NS) as were the odds of extrapyramidal symptoms (OR=3.35, $p<0.0001$). The review reported no clinically significant changes in laboratory values or blood pressure in seven studies. Blood pressure was elevated in the risperidone group in one study. In studies comparing risperidone at different doses or with other agents (pimozide, clonidine, haloperidol), children in the risperidone arms had weight gain and extrapyramidal symptoms that were typically not significantly different from the comparison group, though higher doses of risperidone were associated with greater weight gain and movement symptoms.

In a meta-analysis of three studies of quetiapine versus placebo (including the Connor 2008[180] RCT included in the current review), weight gain, but not prolactin levels, was significantly higher in the quetiapine group (mean difference: 1.41 kg, 95% CI: 1.01 to 1.81). Triglyceride levels, blood pressure, and heart rate were significantly elevated in the quetiapine group compared with placebo in one RCT. The review also included nine RCTs assessing aripiprazole, five of which were combined in meta-analyses. Mean weight gain (mean difference: 0.85 kg, 95% CI: 0.57 to 1.13, $p<0.00001$) and BMI increase (mean difference: 0.27 kg/m^2 95%

CI: 0.11 to 0.42, p=0.0007) were higher in aripiprazole groups compared with placebo, and the odds of weight gain were significantly higher in the treatment group (OR=3.66, p=0.0003). Lipids and ECG values did not differ significantly between groups.

Significant risk of metabolic effects has also been demonstrated to be elevated in large database analyses.[225] Indeed, given the methodologic challenges to reviewing harms in RCTs that are noted above, observational studies such as these are likely to provide more precise estimates of harms. They unfortunately are not necessarily limited to the population of interest in our review, and provide little detailed clinical information.

Harms of stimulants, including methylphenidate and amphetamine salts, which are typically used to treat ADHD and commonly used for DBD, include delay of sleep and anorexia, particularly at higher dosage in the included study. The FDA package insert includes a warning that methylphenidate has been associated with sudden cardiac death in children with existing cardiac abnormalities.

Nonstimulants, including atomoxetine and guanfacine, were associated with increased rates of headache, somnolence, and anorexia.

None of these studies described here, however, explicitly weigh the benefits achieved against these harms, and clinicians and families need to do so including both effectiveness and harms evidence.

KQ6. Modifiers of Effectiveness of Interventions

This question was divided into sub-questions about variations in intervention effectiveness due to a) patient characteristics, b) characteristics of the disorder, c) patient treatment history, and d) treatment characteristics. Although studies examining each of these questions were identified, it is unclear if any of the identified studies were adequately powered to answer these questions.

Regarding variations in the effectiveness of psychosocial interventions due to patient characteristics, it is important to note that most studies included relatively homogeneous age groups (e.g., preschool, school, or adolescent children). That studies were restricted to specific age groups implies widespread, tacit acceptance of the idea that intervention effectiveness varies by child age. At the same time, this aspect of study design limits the ability of included studies to examine this issue. The most commonly examined patient characteristics include child gender, characteristics of the child's mother, and characteristics of the child's family. In general, results were inconsistent and additional examination of these issues is warranted. None of the studies examining pharmacologic interventions addressed the potential for variations in treatment effectiveness based on patient characteristics.

The most commonly examined characteristic of disruptive behavior disorders that was examined for its potential to moderate the effectiveness of psychosocial interventions is the severity of a child's disruptive behaviors at baseline. Results were inconsistent. Difficult temperament and psychopathy were associated with treatment effectiveness in studies with pre-kindergarten age children and studies with teenage children, respectively. More examination of these characteristics is needed.

The severity of a child's disruptive behaviors at baseline and the presence ODD or CD comorbid with ADHD were the characteristics of the disorder that studies of pharmacologic interventions were most likely to examine for their association with differential treatment effectiveness. In general, more disruptive behavior at baseline was associated with greater treatment effectiveness. It is unclear, however, if changes in non-ADHD disruptive behaviors are

independent of changes in ADHD symptoms because of the high prevalence of comorbidity in the study populations.

No studies evaluated variations in the effectiveness of psychosocial interventions due to patient treatment history. One study of atomoxetine indicated that prior treatment with a stimulant was associated with a larger treatment response to atomoxetine.

Studies of psychosocial interventions evaluated variation due to treatment characteristics based on dose – defined by some measure of treatment attendance – and, for interventions including a parent component either alone or in combination with other components, based on whether changing parenting practices mediated intervention effectiveness. The studies defining dose either as session attendance or as homework completion consistently reported greater intervention effects for children whose parents participated more. Similarly, studies examining whether changes in parenting practices were associated with treatment effectiveness consistently provided some support that they were. This is consistent with results from prior reviews.[226]

In pharmacologic studies, the role of baseline severity was inconsistent, with no mitigating effect of severity for nonstimulants, but greater effect associated with greater baseline severity in one RCT of the stimulant mixed amphetamine salts ER.[182] It is not clear if treatment-related changes in ODD symptoms are independent of changes in ADHD symptoms in this population. One study of atomoxetine[176] used a path analysis to evaluate if the treatment effect on ODD symptoms were influenced through the treatment effect on ADHD and/or CD symptoms; they found a nonadditive effect, implying a negative direct effect of atomoxetine on ODD symptoms. In a post hoc analysis of another atomoxetine RCT, authors found that the percent reduction from baseline to endpoint in oppositional symptoms (CPRS-R:L ODD subscale) and ADHD symptoms were highly correlated (r=0.74).

Findings in Relationship to What Is Already Known

We searched for systematic reviews published between 2005 and 2014. We evaluated each for relevance to our Key Questions using the review PICOTS (Appendix B).We identified 22 reviews assessing the effectiveness of psychosocial interventions and two reviews assessing the effectiveness of pharmacologic interventions.

The reviews of psychosocial interventions included two types: reviews of literature regarding specific interventions such as MST and reviews of more general interventions. These reviews did not address potential harms of psychosocial interventions. The two reviews of pharmacologic interventions addressed the effectiveness of atypical antipsychotic medications, though they were not specific to populations of children treated for disruptive behaviors. We describe information about harms from these two reviews (and one additional review that reported harms only) in KQ5 above.

Existing Reviews of Psychosocial Interventions

Of the 22 identified systematic reviews or meta-analyses of psychosocial interventions, we identified one review specific to the MST literature, one review specific to the CBT literature, two reviews specific to the Triple P literature, one review of Triple P and PCIT, 11 more general reviews, and one review of existing reviews. It is important to note that these reviews may include studies not included in the current review due to different study inclusion and exclusion criteria.

Reviews of MST Literature

A Cochrane review included eight RCTs of MST for behavioral and emotional problems in children between the ages of 10 and 17 years.[227] Few studies addressed outcomes related to externalizing behaviors, but an analysis of three studies reporting CBCL Externalizing scales showed pooled results were not significant (standardized mean difference: −0.18, 95% CI: −0.46 to 0.09). This review concluded that there is inconclusive evidence of the effectiveness of MST as compared to other interventions.

Reviews of CBT Literature

One meta-analysis included six studies of CBT for violent behavior and reported limited effects of CBT on child behavior (effect size: −0.094), with decreasing effects reported over time as outcome data accumulated.[228] In a cumulative analysis, effect sizes decreased from 0 to −0.95. This review concluded that this is a medium effect and called for more research into the effectiveness of CBT for violent behavior.

Reviews of Triple P Literature

There were two reviews of the Triple P literature.[229,230] Both of these reviews were meta-analyses and together reported on more than 100 randomized, nonrandomized, and uncontrolled studies.[229,230] These reviews both reported small to medium effect sizes for parenting outcomes (0.38 to 0.57), child behavior outcomes (0.35 to 0.52), and parental wellbeing/satisfaction (0.17 to 0.55) over both the short- and long-term.

These reviews also examined potential moderators. One of these reviews examined if factors related to the specific design of the version of the Triple P program that was implemented (group vs. individual) and reported no consistent effect modification by design.[229] This review also reported that treatment effects were consistently lower when measured by father reports than those of mothers, and that younger child age was associated with greater treatment effectiveness. Neither level of initial behavioral severity nor child gender were significant predictors of outcomes. Program completion was also not associated with the effect size.[229]

The other review reported that Triple P level and Triple P as a treatment (vs. Triple P as a preventative intervention) were associated with higher effect sizes.[230] Online Triple P had the largest effect sizes for child outcomes; the online and group versions of Triple P had the largest effect sizes for parental relationship outcomes. Study power also moderated treatment effects such that higher effect sizes were found for studies with less than 35 participants in the smallest group compared to studies with greater than 35 participants in the smallest group. Significant effect sizes were found for studies with larger sample sizes. This review also reported that the initial severity of child behaviors moderated effects on parental relationship outcomes. This review also noted that Triple P studies that did not include involvement of a developer of the program (n = 31) still produced significant intervention effects on child outcomes.

Reviews of Triple P and PCIT

One meta-analysis examined the effects of PCIT (n = 13 studies) and Triple P (n = 11 studies) on parent-reported child problem behaviors.[231] Children were in the clinical or borderline range for disruptive behaviors in most (but not all) of the studies, and effect sizes in studies reporting between-group comparisons ranged from −1.59 to 5.67 across parent, teacher, father, and observation measures and control groups for PCIT. All forms of PCIT except the abbreviated version had a significant short-term effect on parent-reported child behaviors.

Effect sizes ranged from −0.96 to −0.02 for Triple P across informants and all formats (group, self-directed, etc.). The effect size for PCIT (−1.45) was significantly higher than those for self-directed (−0.51), group (−0.67), and individual Triple P (−0.69) but not for media or enhanced Triple P. Effects sizes for observed outcomes were not significantly different from PCIT and any form of Triple P. Negative parenting behaviors were also improved with both PCIT and Triple P. The review notes that limited evidence addresses effects over the longer term.

More General Reviews

There were 11 general reviews, not restricted to literature about specific interventions. These reviews included RCTs, controlled trials, and quasi-experimental studies published in any country, including studies dating to the 1980s. As in the current review, participants in the studies included in prior systematic reviews were mostly male and typically Caucasian. Most of the included studies were small, with short-term (≤ 6 months) followup. Studies were generally of moderate methodological quality, with reporting of family characteristics, allocation concealment, and randomization methods generally noted as limited. Reviews described variations in inclusion criteria (e.g., requirement of DSM diagnosis of a DBD, only parent-reported problem behaviors) and recruitment methods. A brief summary of each of these reviews is included below.

One meta-analysis included 28 RCTs for a total of 2239 children with disruptive behaviors between the ages of 2 and 12 years.[59] Fourteen studies assessed variations of the IY program, nine studies evaluated the Triple P, two studies evaluated PCIT, and three studies assessed other approaches such as "Project TEAM." The investigators rated six of the studies as low or moderate risk of bias. Overall, the studies varied in terms of how they defined their target population with studies using clinical cut-off levels on established measures, DSM diagnoses, or general parent-reported behaviors to establish inclusion. Reporting of parent and family characteristics also varied across studies. Child disruptive behaviors measured on the ECBI Intensity and Problem scales were significantly ($p<0.001$) reduced in active treatment arms compared with control (weighted mean differences of −20.90, 95% CI: −26.26 to −15.53 and −6.03 95% CI: −7.70 to −4.36, respectively). CBCL Externalizing scores and Strengths and Difficulties Questionnaire (SDQ) Conduct scales were also significantly improved in active treatment arms compared with control groups.

Another meta-analyses of 57 RCTs of parenting programs for child disruptive behaviors reported similar results.[55] In combined analyses of ECBI-Intensity and CBCL scales reported in 24 of these studies, children in the parent management training intervention arms had improved outcomes compared with children in comparison arms (standardized mean difference: −0.67, 95% CI: −0.91 to −0.42). Investigators' analysis of other outcomes reported in 36 studies aligned with these meta-analysis findings: for 100 of 170 child behavior outcomes, outcomes were significantly improved in children in treatment groups compared with those in control groups. Meta-analysis of independent observations in seven studies also demonstrated significantly improved outcomes for children in active treatment groups versus control groups (standardized mean difference: −0.44, 95% CI: −0.66 to −0.23).

A United Kingdom National Health Service review of 37 RCTs of parenting interventions for children with conduct disorder also reported consistent evidence for the short-term effectiveness of parent training programs compared with control groups.[232] Six included studies were assessed as good or adequate quality; the other 31 studies were rated as poor or very poor quality. Pooled

estimates demonstrated significant improvement in treatment groups compared with control on the ECBI, CBCL, and in observer coding of parent-child interactions, while differences between the parent management approaches studies were not consistent.

Another review of seven studies of primarily parent management approaches addressed intervention for children with ODD and reported the greatest effects on child behavior when interventions targeted parents (standardized mean difference: 1.06; 95% CI: 0.70 to 1.41), with smaller effects if only children were targeted (standardized mean difference: 0.93; 95% CI: 0.52 to 1.34).[233]

A meta-analysis including 79 studies reporting on children with externalizing behaviors noted a mean weighted effect size of 0.30 (95% CI: 0.21 to 0.39) for end of treatment child behaviors in studies with comparison groups, 0.68 (95% CI: 0.59 to 0.77) for within group comparison studies, and 0.54 (95% CI: 0.43 to 0.65) in single subject studies.[234] Effect sizes at followup were 0.40 for between-group designs, 0.79 for within groups, and 1.74 for single subject designs. Modifiers across each study type varied, but child age, method of treatment delivery, use of randomization, use of reliability assessment, and number of treatment sessions were significant modifiers of effects in between-group studies, with studies that included children age 9 to 11 years (n = 2) had larger effects. Those using individual consultation and controlled learning and those using non-random assignment also had larger effects as did those not reporting a reliability assessment. Finally, studies using between one and five treatment sessions had greater effect sizes than those using more sessions.

Another meta-analysis of 63 studies including children with DBD reported overall effect sizes of 0.42 for child behavior outcomes, 0.47 for parent behaviors, and 0.53 for parental perceptions in the short term and smaller effect sizes in the longer term.[235] Children from families with lower socioeconomic status had less improvement of behaviors than did the children from families with higher socioeconomic status ($p<0.01$), as did those in studies with groups with more single parents compared to those with fewer single parents ($p<0.01$). Children with clinically significant baseline levels of disruptive behavior had greater change than did children without such clinically significant behaviors ($p<0.05$). Socioeconomic status also significantly moderated parent outcomes, with lower socioeconomic status associated with poorer outcomes. In contrast to our findings, treatment modalities involving only the parent were associated with greater positive change than those delivering interventions to the child separately or using a multisystem approach ($p<0.05$). Change in parent perceptions (confidence, stress) was also greater with parent-only interventions compared with those involving parents and children ($p<0.05$).

One meta-analysis included 33 studies of psychosocial interventions (including but not limited to behavior therapy, family therapy, CBT, psychodynamic therapy) with untreated comparison groups.[236] These studies included many of the IY and PCIT studies also included in the other meta-analyses, but this review did not separately report results for any specific intervention group. Effect sizes in all 33 studies indicated improvement after treatment in active treatment vs. control arms with an overall mean weighted effect size of 0.62 (95% CI: 0.49 to 0.76). Smaller sample sizes were associated with larger effect sizes as compared to studies with larger sample sizes.

Another meta-analysis of broadly defined psychosocial interventions (including behavioral approaches and non-behavioral approaches such as family systems interventions and nondirective counseling, and named interventions such as variations of IY and PCIT) included 36 RCTs (n = 3042 children).[237] The overall effect size (effect sizes for aggression,

oppositionality, impulsivity, and general externalizing behaviors combined) for psychosocial treatments on disruptive behaviors was 0.82 (SE=0.10, 95% CI: 0.63 to 1.01). Significant moderators of effect included symptom type, with externalizing symptoms showing the largest response. Treatment as usual comparators also yielded larger effects than no treatment control groups, and no treatment controls yielded greater effects than "education, support, and attention" controls. Behavioral treatments demonstrated larger effects on behavioral symptoms than did non-behavioral interventions.

A review including 28 studies including 16 psychosocial interventions for children with disruptive behavior disorders for which there was an evidence base. The authors summarized their results by classifying interventions according to Chambless criteria,[238] as "well established" (e.g., MPTO), "probably efficacious" (e.g., Group Assertiveness Training (peer and counselor led), Anger Control training, Helping the Noncompliant Child, IY (child, parent, and multiple component), Multidimensional Treatment Foster Care, PCIT, Problem Solving Skills Training (multiple versions), Rational-Emotive Mental Health Program, and Triple P standard and enhanced programs), or "possibly efficacious" (e.g., IY with teacher training components, Triple P standard group treatment, First Step to Success, Reaching Educators, Children, and Parents, Self-Administered Treatment Plus Signal Seat, and Group Anger Control Training). The investigators recommend parent training as the first line treatment for young children and that direct child training or multicomponent approaches be used with older children.

A meta-analysis including 71 studies of interventions categorized as either parent management training or CBT reported positive outcomes associated with parent management training interventions.[239] The mean effect size for both interventions combined (also combining parent and teacher-reported measures and observation outcomes) was 0.40 (95% CI: 0.34 to 0.47). The mean effect size for parent management training alone was 0.47 (95% CI: 0.34 to 0.61) and 0.35 (95% CI: 0.25 to 0.47) for CBT alone. In comparisons of effect sizes in children between ages 6 and 12 (ages were too widely varying to allow other comparisons), the effect size for parent management training (0.45, 95% CI: 0.28 to 0.60) was significantly greater than that of CBT (0.23, 95% CI: 0.11 to 0.32) in analyses not controlling for intervention setting (e.g., clinic, school). The difference was not significant in analyses controlling for setting. In moderator analyses, child age was not significantly associated with outcomes of parent management, but older child age was associated with better outcomes in studies of CBT.

A Campbell Collaboration review and meta-analysis included 55 RCTs including children age 5 or younger and focused on prevention of child behaviors such as delinquency, crime, and antisocial behavior.[240] Most studies (n = 47) evaluated programs included in the current review such as IY variations, PCIT, and Triple-P. Eight trials assessed home visits by clinicians. Most studies were in the United States (n = 38), and most (n = 37) included fewer than 100 children. The overall weighted mean effect size across all 55 studies was 0.35, a small to medium effect for reducing child behavior problems. Differences between parent training and home visit programs were not significant. In regression analyses, older studies, smaller studies (n<100), and U.S. studies were more likely to have larger effect sizes. Meta-analyses also suggested the presence of publication bias.

Reviews That Include Existing Reviews

Findings in a review of RCTs, quasi-experimental studies, and systematic reviews and meta-analyses conducted for the U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration's (SAMHSA) Assessing the Evidence Base series of

literature reviews also align with findings in prior syntheses.[241] The SAMHSA review reports a high level of evidence (defined as confidence in the reported outcomes based on three or more well-conducted RCTs or two RCTs and well-conducted quasi-experimental studies) for both IY and PCIT, noting well-designed RCTs of adequate power, manualized approaches, reliable outcome measurement, and replication in multiple studies. IY and PCIT were also associated with improved externalizing behavior outcomes across age ranges and populations when compared with waitlist control groups, and the review concludes that abbreviated or adapted versions of IY and PCIT are also promising.

Summary of Evidence From Existing Reviews on Moderators and Mediators of Effectiveness

A number of existing reviews examined questions related to moderation and/or mediation of intervention effectiveness including a wide range of demographic and clinical variables. Most of the examined demographic and family process variables were not consistently identified as moderators with the strongest evidence appearing to include severity of baseline child disruptive behaviors, child age, and socioeconomic status.

Regarding the severity of baseline child disruptive behaviors, three existing reviews presented evidence suggesting that severity moderates intervention effectiveness, [230,235,242] and one review did not.[229] One quasi-systematic review identified six studies assessing baseline child behavior as a moderator. In four of these six studies, higher baseline levels of problem behavior were associated with better outcomes but the other two studies did not.[243] Two previous reviews cited evidence that child age moderated intervention effectiveness, [229,234] and two studies reported that family socioeconomic status also moderates intervention effectiveness.[242,244]

Finally, one quasi-systematic review specifically examined if parenting was a mediator of the effectiveness of behavioral parent training for child disruptive behaviors and provided some, but not overwhelming, support for this hypothesis.[226]

Existing Reviews of Pharmacological Interventions

We identified two reviews of the effectiveness of pharmacologic interventions for children, though not all of the included studies were specific to populations of children treated for disruptive behaviors. We describe information about harms from these two reviews (and one additional review that reported harms only) in KQ5 above.

One Cochrane review of atypical antipsychotics for disruptive behavior disorders included eight RCTs (7 of risperidone and 1 of quetiapine) and reported limited evidence of effectiveness. In one analysis, scores on the Aberrant Behavior Checklist were 6.49 units lower, which may be clinically significant, and the investigators considered the difference of 8.61 points on the Nisonger Child Behavior scale as likely clinically significant.[49]

In the other included review of pharmacologic interventions, an AHRQ-funded review of antipsychotic use in children and young adults, strength of the evidence was insufficient for comparisons of first versus second-generation antipsychotics, first versus first generation, and first generation versus placebo.[52] In eight studies of antipsychotics for treatment of disruptive behavior disorders (including 682 children treated for between 4 weeks to 6 months), strength of the evidence was moderate for positive effects of antipsychotics on behavior symptoms and low for positive effects on aggression and anxiety.

Applicability

KQ1. Psychosocial Interventions

Applicability for this literature is largely dependent on the target population and feasibility of the interventions in real-world clinical settings. Our target population was primarily defined by child age and type of disruptive behavior problem. Included psychosocial interventions excluded preventive interventions, were typically multi-faceted and heterogeneous within broad intervention categories, and can be resource intensive relative to time, money, and personnel in the clinical setting.

Approximately half of the studies of psychosocial interventions for child disruptive behaviors were of school-age children, about 30 percent were with preschool-age children, and approximately 20 percent were with teenagers. We defined a study as focusing on school-age children if it had a sample with a mean age between 5 and 12 years. We established 5 years of age as the lower bound because this is the age at which children typically begin attending kindergarten in the United States. We established 12 years of age as the upper bound because 13 years is regarded as the beginning of adolescence in casual parlance. For precisely these reasons, the age group classification we used is somewhat arbitrary, specific to the United States context, and has face validity in the United States. At the same time, many studies of child samples with a mean age between 5 and 12 years also included children with age less than 5 or greater than 12 years.

In addition to the age definition, our definition of the target population included children with disruptive behaviors receiving treatment in healthcare settings. We did not restrict our study population to children meeting formal diagnostic criteria for a disruptive behavior disorder. Rather, we allowed children without a diagnosed DBD but with disruptive behaviors above a measure-specific threshold on a well-validated measure of disruptive behavior to be included. This may limit applicability of our findings because in real-world clinical settings third-party payers may only reimburse for services regarded as medically necessary. We excluded studies of preventive interventions for an at-risk population because our review was focused on studies of individuals who met a clinical threshold for a disruptive behavior disorder.

A potential issue for applicability of these findings is whether patients are able to access and pay for them if insurance does not cover them. However, an evaluation of costs was beyond the scope of this report as it was set up. Applicability of our findings is also limited by restricted access to some of the interventions most commonly examined in the studies included in this review in real-world clinical settings. Many of the included studies were conducted in the outpatient setting and carried out at academic medical centers in the United States. To give just one example, although there was relatively strong evidence in favor of the effectiveness of MST for disruptive behaviors in teenagers, MST is often not available in real-world clinical settings. This is consistent with a growing literature on the challenges of transporting evidence-based multicomponent interventions into real-world clinical settings with fidelity.

Many included studies were also conducted by the intervention developer or by other individuals with a vested interest in the intervention. Although this aspect of study design may be required to ensure treatment fidelity or at least make it more likely that interventions are delivered with fidelity to the model, it may also create a need for independent validation of study results.

KQ2. Pharmacologic Interventions

The populations studied the studies of pharmacologic interventions for disruptive behavior disorders were almost exclusively male and between the ages of 6 and 18 years. All of the studies were very small, and results may not be broadly generalizable. None of the interventions have a specific indication for disruptive behaviors, although they are used for these conditions in the United States. Interventions included antipsychotic drugs, an antiepileptic drug, and ADHD drugs (both stimulants and nonstimulants). Of particular importance, all but one study on pharmacologic interventions were funding wholly or partially by a pharmaceutical company, or were conducted by individuals who are highly supported by those companies. It is difficult to assess the degree to which these drugs are or are not widely available. The studies also did not address the common concern of polypharmacy and thus there may be limited ability to assess applicability as well as safety concerns in highly complex cases. Polypharmacy with two or more antipsychotic drugs is a commonly used indicator of poor quality care although it clearly occurs. A better understanding of the prevalence, circumstances, and implications of polypharmacy is needed.

In reality, many if not most children and adolescents seeking treatment for disruptive behaviors may have multiple co-diagnoses and other complex challenges. The applicability of this set of studies, in which we limited the population to a specific focus on disruptive behavior treatment, may not capture the overall effect of pharmacologic intervention on these children's lives overall, nor are they likely to be applicable to highly complex cases. The use of pharmacologic interventions for outcomes in cases, for example, of ADHD, autism or other conditions like bipolar is addressed in other reviews.

Strength of Evidence

We assessed strength of evidence for the effectiveness of interventions using the qualitative and quantitative approaches described in the Methods section. Overall, the evidence to answer Key Questions about interventions for children with disruptive behavior disorders was insufficient to moderate. We summarize the strength of the evidence and provide the assessment of the risk of bias, consistency of findings across trials, directness of the evidence, and precision of the estimate provided by the literature (Tables 48-51).

Table 48. Strength of evidence for effects of psychosocial interventions targeting parenting practices on parent-reported changes in disruptive behaviors in preschool children with DBD

Intervention Category	Study, Risk of Bias (Participants)	Study Limitations	Consistency	Directness	Precision	Reporting	*SOE* Findings and Magnitude of Effect[a]
Child Only (n = 0)	NA	NA	NA	NA	NA	NA	Insufficient
Parent Only (n = 14)	RCT: 1 low,[138] 7 moderate,[93,119,129,135,139,140,155] 5 high[95,102,127,141,145] (1466) Cohort: 1 moderate[87] (144)	Medium	Consistent	Direct	Precise	Undetected	Moderate SOE for positive effects of intervention on child behavior. Outcomes consistently improved in parenting intervention arms compared with waitlist or treatment as usual controls. Differences between modified versions of the same intervention were typically not significant. Outcomes measured on parent-reported scales, which are a reliable indicator of change in this population.
Multicomponent (n = 9)	RCT: 1 low,[99] 3 moderate,[109,114,133] 5 high,[98,107,112,153,154] (401)	Medium	Consistent	Direct	Precise	Undetected	Moderate SOE for positive effects of intervention on child behavior. Outcomes consistently improved in parenting intervention arms compared with waitlist or treatment as usual controls. Differences between modified versions of the same intervention were typically not significant. Outcomes measured on parent-reported scales, which are a reliable indicator of change in this population.

Table 49. Strength of evidence for effects of psychosocial interventions targeting parenting practices on parent-reported ratings of disruptive behaviors in school-age children with DBD

Intervention Category	Studies, Risk of Bias (Participants)	Study Limitations	Consistency	Directness	Precision	Reporting	*SOE* Findings and Magnitude of Effect
Child Only (n = 1)	RCT: 1 moderate[132] (97)	Medium	NA	Direct	NA	Undetected	Insufficient due to a single study.
Parent Only (n = 11)	RCT: 1 low,[121] 5 moderate,[113,122,125,130,147] 2 high[117,118] (995) Cohort: 3 high[88,90,91] (334)	Medium	Consistent	Direct	Precise	Undetected	Moderate SOE for positive effects of intervention on child behavior change. Outcomes significantly improved in intervention groups vs. control but differences between modified versions of the same intervention were not significant. Outcomes measured on parent-reported scales, which are a reliable indicator of change in this population.
Multicomponent (n = 17)	RCT: 1 low,[123] 11 moderate,[96,97,101,103,105,108,110,126,128,131,137] 3 high[100,134,165] (1685) Cohort: 1 high[89] 1 moderate[92] (474)	Medium	Inconsistent	Direct	Precise	Undetected	Low SOE for positive effects of intervention on child behavior change. Children improved from baseline in most active treatment arms but between group changes not consistently significantly different. Ratings on sub-scales (e.g., EBCI-Intensity, EBCI-Problem) not always consistent.

Table 50. Strength of evidence for the effect of psychosocial interventions targeting parenting practices on parent-reported ratings of disruptive behaviors in teenage children with DBD

Intervention Category	Studies, Risk of Bias (Participants)	Study Limitations	Consistency	Directness	Precision	Reporting	*SOE* Findings and Magnitude of Effect
Child Only (n = 1)	RCT: 1 High[104] (93)	High	NA	Direct	NA	Undetected	Insufficient SOE due to single study with high study limitations.
Parent Only (n = 0)	NA	NA	NA	NA	NA	NA	Insufficient.
Multicomponent (n = 13)	RCT: 4 Low,[120,124,142,143], 5 Moderate,[94,111,116,144,146] 3 High[106,115,136] (1294) Cohort: 1 High[86] (192)	Medium	Consistent	Direct	Precise	Undetected	Moderate SOE for positive effects of intervention on child behavior change. Most studies reported improved outcomes in treatment arms versus control arms. Differences between modified versions of the same intervention were typically not significant. Outcomes measured on parent-reported scales, which are a reliable indicator of change in this population.

Table 51. Strength of evidence for pharmacologic interventions

Intervention: Outcome	Design: Studies (Participants)	Limitations	Consistency	Directness	Precision	Reporting	*SOE* Magnitude of Effect
Antipsychotics: Disruptive Behavior	RCT: 3 (374)[180,183,186]	High risk of bias: 1[183] Moderate risk of bias: 2[180,181] Low risk of bias: 1[186]	Consistent	Direct	Precise	Undetected	Moderate SOE for the effectiveness of antipsychotics in achieving statistically significant improvements in measures of disruptive behaviors over the short term. Studies were funded by industry and should be replicated by groups without appearance of conflict.
Antipsychotics: Aggression	RCT: 3 (64)[180,181,186] Cohort: 1 (36)[188]	Moderate: 2[180,181] Low: 1[186] High: 1 (36)[188]	Inconsistent	Direct	Imprecise	Undetected	Insufficient SOE based on inconsistent and imprecise outcomes, and small numbers of participants.
Stimulants[a]	RCT: 2 (391)[182,187]	High risk of bias: 2[182,187]	Consistent	Direct	Precise	Undetected	Low SOE based on only two high risk of bias studies that used different outcome measures.
Nonstimulants[b]	RCT: 3 (537)[176,177,179]	High risk of bias: 1[179] Moderate risk of bias: 2[176,177]	Consistent	Direct	Precise	Undetected	Moderate SOE for the effect of nonstimulants on disruptive behaviors with 3 studies, adequate numbers, and statistically significant change scores of 0.59 to 0.69.

Table 51. Strength of evidence for pharmacologic interventions (continued)

Intervention: Outcome	Design: Studies (Participants)	Limitations	Consistency	Directness	Precision	Reporting	*SOE* Magnitude of Effect
Divalproex	RCT: 3 (108)[178,184,185]	Moderate risk of bias: 3[178,184,185]	Consistent	Direct	Precise	Undetected	Low SOE for improvement or remission associated with aggressive behavior, with "success" more than threefold likely in treated versus untreated. SOE remains low due to only 3 small studies with moderate risk of bias. Insufficient evidence that higher doses are more effective than lower doses given one study with moderate risk of bias.

[a]Includes methylphenidate and amphetamine
[b]Includes atomoxetine and guanfacine

Limitations

Limitations of This Review

This was a focused review on treatments for recognized disruptive behavior disorders at the individual level. Our focus was on treatments within a clinical setting or that might be a referral from a clinical setting. Therefore, we did not include ecologic approaches and psychosocial interventions that have been studied in settings such as juvenile delinquency settings and schools. These are important components of the overall therapeutic environment for disruptive behavior disorders and have been reviewed elsewhere.

We classified a heterogeneous group of interventions into the three broad categories of interventions that only include a child component, interventions that only include a parent component, or multi-component interventions. We defined multicomponent interventions as those that included two or more of a child component, parent component, or other component (e.g., teacher component, family together component). To account for the fact these treatment categories are broad, encompassing a range of specific interventions, each component was modeled as a random effect. This allowed for variation in treatment effect within each class. It is also worth noting that we classified PCIT as a multi-component intervention because, as its name suggests, the focus of the intervention is on the parent-child interaction and includes the parent and child engaged together in activities. Out of concern that PCIT in particular may also reasonably be classified as an intervention with only a parent component, we ran our quantitative model under both classifications (i.e., with PCIT categorized as a multi-component intervention and as an intervention with only a parent component). Classifying PCIT as an intervention with only a parent component did not significantly change our meta-analysis results, although point estimates of effect were nominally different.

We also excluded studies that focused on the treatment of other psychiatric conditions likely to have comorbid features of DBD. These would include, for example, ADHD, autism, and bipolar disorder. These are important and prevalent conditions and our review is intended to provide evidence on a very specific set of interventions in a defined group of participants. Clinical decisions need to be made with all of the available information, potentially from other reviews, particularly in complex clinical scenarios.

We did not limit inclusion to studies of individuals with a DSM diagnosis of DBD, but we did limit to those studies that provided some evidence that participants were beyond a validated clinical cutoff. Given the diversity of DBDs and a lack of consistent approach to assessing or reporting them, this is not a perfect approach. It is possible that some studies that did focus on DBDs were missed due to the reporting of the papers. We also focused on the outcomes that were by far the most commonly reported in the literature – e.g., parent reports of their child's disruptive behaviors – via measures assessing externalizing behaviors. Functional outcomes are also important. We recognize that parent reports of their child's disruptive behaviors are potentially biased, particularly when study designs did not include blinding. We also recognize that there are outcomes of interest such as emotional and psychological states beyond those that we specified in our protocol, but to widen the scope would have been infeasible for this review. Similarly, there is substantial overlap between several other psychological conditions and DBDs, including in particular ADHD. We did not include studies that focused primarily on treating ADHD, although some of these studies may also include evidence about disruptive behaviors as a component of ADHD. There are good reviews of ADHD treatment, including one by AHRQ,[69]

and we would point readers to those as additional information. We did include a number of studies that used traditional ADHD drugs but were focused on the disruptive behaviors themselves.

We were unable to review DBD interventions by etiology, although we understand that disruptive behaviors may stem from many causes (e.g. trauma), and these play into decisions about treatment and therapy.

Limitations of the Evidence Base

KQ1. Psychosocial Interventions

A number of methodological limitations exist in the literature base for child disruptive behavior disorders. First, identifying the target population is difficult. We included in our review both studies of children with a formal diagnosis of a disruptive behavior disorder and children without a formal diagnosis of a disruptive behavior disorder who scored above a clinical cutoff on a well-validated measure of child disruptive behaviors, but lack of detail in reporting by authors makes it challenging to fully and accurately characterize the populations in the studies.

Second, although most included studies were RCTs, overall the literature suffered from a lack of consistent and complete reporting. In particular, primary outcomes are rarely identified, and random sequence generation and allocation concealment rarely described. In addition, there was frequently no attempt to achieve blinding. Although there are well-recognized and valid reasons that achieving this level of control in the studies is challenging, if not impossible, it does bring some degree of potential risk of bias into the literature as a whole.

Third, the field lacks consensus on the most important outcomes. Few studies measure similar outcomes for synthesis. Methodologically, outcomes such as direct observation by a blinded and independent observer are arguably the most valid. However, direct observations can be expensive and are not always logistically feasible. From the perspective of patient-centered outcomes research, we believe that there is a strong argument in this literature to be made in favor of the importance of parent reported outcomes. However, most of the studied interventions included a parent component either alone or in combination with other components which introduces a potential risk of bias especially considering that blinding was not always feasible, and when parent reported outcomes were included multiple measures of similar constructs were used within and across studies. The reliance of the literature on parent reported outcomes and their potential for bias is a significant limitation of the evidence base.

Fourth, conflict of interest is a concern in this evidence base. Most of the studies evaluating a psychosocial intervention for a child disruptive behavior included in this review were conducted either by the developer of the intervention or by an “intellectual descendant” of the developer. Although it is understandable for this to be the case (much like it is understandable to see industry-sponsored clinical drug trials), the strength of the evidence for this body of literature would be strengthened with more studies independently evaluating the interventions.

Fifth, there are few direct comparisons of individual interventions. Specific interventions were most often compared to a waitlist control group or treatment as usual (variably described). When comparisons of active treatments were included, it was most often a comparison of different versions of a specific intervention. Further, results from mixed models are not always presented in a straightforward manner, making it very difficult to tease out effects of specific treatment approaches.

KQ2. Pharmacologic Interventions

There were surprisingly few studies focused on treating disruptive behaviors with pharmacologic interventions, which reflects the fact that these drugs are frequently used off label and without a research basis for their use in this particular set of disorders. Indications for the drugs reviewed here include a range of conditions, including but not limited to ADHD, schizophrenia, bipolar disorder, and seizures (complete list in Appendix I). As such, many of the studies include mixed populations and report outcomes of overlapping symptoms (e.g. of ADHD and DBD) making it difficult to discern the degree to which the mitigation of ADHD, for example, is in fact driving the results. Most of the studies in this section were small and larger studies are clearly needed.

Finally, it is a particular weakness that almost all studies were funded by the pharmaceutical company making the drug being studied. There is a clear need for replication and for independently funded studies.

KQ3 and KQ4. Combined Interventions

There were no studies to evaluate the efficacy of both behavioral and pharmacologic interventions compared to pharmacologic or behavioral interventions alone. Given that the clinical reality for many, if not most, families is that they use a multipronged approach for treatment of their children with DBDs, these studies are needed.

Future Research Needs

Research needs are both substantive and methodologic, and include both conduct and reporting of research. As noted above, randomization and allocation approaches were consistently not adequately described, and blinding was not attempted or addressed in much of the psychosocial literature. Future research should also clearly describe the duration of time from baseline to post-treatment and post-treatment to followup, and more clearly describe results from mixed models. Because the intervention developer is often the researcher, existing research must be replicated, as the lack of replication introduces the potential for a risk of bias analogous to that introduced by industry-sponsored trials of pharmaceutical interventions.

There is a need for specific, head-to-head comparisons of psychosocial interventions, evaluate the effectiveness of psychosocial interventions as compared to pharmacologic interventions (KQ3), and the effectiveness of combined psychosocial and pharmacologic intervention (KQ4). Additionally, prospective longitudinal studies examining implementation of these interventions in real-world community practice, including cultural adaptations, are also needed. End users urgently need this information to make informed decisions about which treatments to seek for their children. Clinicians need answers to these questions to decide which interventions to be trained to deliver and to recommend to their patients. Policymakers need this information to determine how to incentivize the provision of care for which there is the most evidence of effectiveness.

Future research should also clearly identify the target population and address the portability of studied interventions from predominantly university research clinics to real-world clinical settings. In the United States, disruptive behaviors are more prevalent among children receiving publicly funded care, and who are therefore likely to receive treatment in clinical settings such as community mental health centers. This group of young people may differ in important ways from the children receiving treatment in university-based research clinics. There is a growing

body of literature about the challenges of implementing and disseminating best practices to real-world clinical settings with fidelity.[245]

Implications for Clinical and Policy Decisionmaking

Qualitatively and quantitatively, our review suggests that psychosocial interventions that include a parent component either alone or in combination with other components have the greatest probability of being most effective. This suggests that parents of children with disruptive behavior disorders should seek interventions that include a parent component. Clinicians providing care to this patient population should reconsider their current practices and clinicians referring families to specialty care should look to make referrals to clinicians whose interventions include a parent component. Researchers should consider more rigorously designed evaluations including of the potential harms of psychosocial interventions for this population, and policymakers and third party payers might consider writing clinical practice guidelines and reimbursement strategies that reflect this evidence.

There is less consistent evidence from the pharmacologic literature, but moderate SOE available for the use of antipsychotics and nonstimulant drugs. Parents of children with disruptive behaviors may, in consultation with their healthcare providers, want to consider the potential benefits of these pharmacologic options in the context of what is known about their risks. Many if not most clinicians providing pharmacologic care to this patient population are likely already aware of the potential benefits and harms of associated with use of these medications. Researchers may see potential for additional research on the effectiveness of these medications for this patient population. The implications for policymakers and third party payers are somewhat less clear.

Although we know from studies of other childhood disorders such as depression that combined psychosocial and pharmacologic intervention has benefits over either intervention alone,[246] there is currently insufficient evidence to make similar conclusions for the treatment of children with disruptive behaviors. In reality, families of children with DBDs and the clinicians working with them are likely facing an array of treatment approaches to combat a complex set of symptoms or expressions of psychiatric conditions. This report should be assessed within the context of other reviews and primary literature. It provides evidence for one piece of a complex puzzle.

Conclusions

This review suggests that psychosocial interventions for children with disruptive behavior disorders that are multicomponent interventions or interventions that include only a parent component are likely to be more effective at reducing problem behaviors than psychosocial interventions that include only a child component or treatment as usual. As defined in this study, all multicomponent interventions included a parent component. Thus, it seems likely that a parent component is important. There are very few studies directly supporting the effectiveness of pharmacologic interventions for children with disruptive behavior disorders, but small studies of antipsychotics and stimulants report positive effects in the very short term. There are no studies examining the effectiveness of these interventions in combination with one another. The most commonly reported outcomes are parent-reported outcomes. Long-term and functional outcomes were not consistently reported. There was variability in the duration of long-term followup and functional outcomes reported. To date, treatment research is almost exclusively supported by the pharmaceutical industry. Given the prevalence of DBDs and the need for high

quality data to inform clinical practice, more long-term studies are needed as are studies aimed at treating DBD separate from comorbid ADHD.

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Abbreviations

AABC	Adolescent Antisocial Behavior Checklist
AACAP	American Academy of Child and Adolescent Psychiatry
AARS	Adolescent Anger Rating Scale
AAQ	Barratt Aggressive Acts Questionnaire
ABC	Aberrant Behavior Checklist
ABC-IS	Aberrant Behavior Checklist-Irritability Subscale
ABI	Adaptive Behavior Inventory
ADHD	Attention Deficit Hyperactivity Disorder
AGG	Aggression
AIAQ	Anger Irritability and Aggression Questionnaire
AIAQ	Anger Irritability and Assault Questionnaire
APS	Adolescent Psychopathology Scale
APSD	Antisocial Process Screening Device
AQ or AGQ	Aggression Questionnaire (Buss-Perry Aggression Questionnaire)
ARBS	Adolescent Risk Taking Behavior Scale
ART	Aggression Replacement Training
ATP	Adolescent Transitions Program
ATX	Atomoxetine
BASC	Behavior Assessment System for Children
BASC-2	Behavior Assessment System for Children, Second Edition
BASIC	Behavioral and Affective Skills in Coping
BDHI	Buss-Durkee Hostility Inventory
BPC	Brief Problem Checklist
BPI-01	Behavior Problem Inventory
BSFT	Brief Strategic Family Therapy
CAFAS	Child and Adolescent Functioning Scale
CANS-MH	Child and Adolescent Needs and Strength-Mental Health
CAS	Children’s Aggression Scale
CAS-P	Children’s Aggression Scale, Parent Rated
CAS-T	Children’s Aggression Scale, Teacher Rated
CBCL	Child Behavior Checklist
CBRS	Conners Comprehensive Behavior Rating Scales
CBT	Cognitive-Behavioral Therapy
CBQ	Children’s Behavior Questionnaire
CCNES	Coping with Children’s Negative Emotions Scale
CD	Conduct Disorder
CERT	Center for Education and Research on Mental Health Therapeutics
CGAS	Children’s Global Assessment Scale
CGI-C	Clinical Global Impressions, Change Scores
CGI-I	Clinical Global Impressions, Improvement Item

CGI-S	Clinical Global Impressions, Severity
CI	Confidence Interval
CNS	Central Nervous System
CON	Control
CPPRG	Conduct Problems Prevention Research Group
CPRS	Children's Psychiatric Rating Scale
CPRS	Conners Parent Rating Scale
CPRS-RS	Conners Parent Rating Scale, Revised
CPS	Collaborative Problem Solving
CrPTRC	Conners Parent and Teacher Rating Checklist, Revised Short Form
CRS	Conners Rating Scale
CSBS	Children's Social Behavior Scale
CSI-4	Children Symptom Inventory-4
CT	Child Training
CTRS	Conners Teacher Rating Scale
CWD-A	Adolescents Coping with Depression
CWL	Caregiver Wish List
DARE	Drug Abuse Resistance Education
DBD	Disruptive Behavior Disorder
DB-DOS	Disruptive Behavior Diagnostic Observation Scale
DBD-NOS	Disruptive Behavior Disorder-not otherwise specified
DBR	Direct Behavior Rating
DBS	Disruptive Behavior Scale
DISC	Diagnostic Interview Schedule for Children
DOF	Direct Observation Form
DPICS	Dyadic Parent-Child Interaction Coding System III
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth edition
ECBI	Eyberg Child Behavior Inventory
ECI-4	Early Childhood Inventory-4
EPS	Emergent Extrapyramidal Symptoms
FDA	Food and Drug Administration
FFT	Functional Family Therapy
FSE	Educational Fire Safety Intervention
FT	Family Training
G	Group
GCJS	Global Clinical Judgements Scale
HNC	Helping the Noncompliant Child
HSQ	Home Situations Questionnaire
HVF	Home Visit from a Firefighter
IAB	Interview for Antisocial Behavior
ICD	International Classification of Diseases

IIP-D	Inventory of Interpersonal Problems
INT	Intervention
ITT	Intention to treat
IY	Incredible Years
IY-CT	Incredible Years Child Training
IY-PT	Incredible Years Parent Training
IY-TT	Incredible Years Teacher Training
K-DBDS	Kiddie Disruptive Behavior Disorders Schedule
KQ	Key Question
KSADS	Schedule for Affective Disorders and Schizophrenia for School-Age Children
LHA	Life History of Aggression
LSM	Least Square Mean
MAS XR	Mixed Amphetamine Salts Extended Release
MDD	Major Depressive Disorder
MST	Multisystemic Therapy
MTFC	Multidimensional Treatment Foster Care
N	Number
NA	Not Applicable
NAMCS	National Ambulatory Medical Care Survey
NCBRF	Nisonger Child Behavior Rating Form
ND	No Data
NHAMCS	National Hospital Ambulatory Medical Care Survey
NMA	Network Meta-analysis
NR	Not Reported
NYTRS	New York Teacher Rating Scale for Disruptive and Antisocial Behavior
OAS	Overt Aggression Scale
ODD	Oppositional Defiant Disorder
PAI-A	Personality Assessment Inventory-Adolescent
PATHS	Promoting Alternative Thinking Strategies
PBSS	Positive Behavioral Support System
PCIT	Parent-Child Interaction Therapy
PDR	Parent Daily Report
P-GBI	General Behavior Inventory, Parent Vision
PICOTS	Population, Intervention, Comparator, Outcomes, Timing, Setting
PMT	Parent Management Training
PMT-O	Parent Management Training-Oregon
POS	Play Observation
PRA	Proactive and Reactive Aggression Scale
PS	Parenting Scale
PSC-17	Pediatric Symptom Checklist
PSI	Parenting Stress Index

PSI/SF	Parenting Stress Index Short Version
PSST	Problem-Solving Skills Training
PT	Parent Training
QOL	Quality of Life
QRBC	Quay Revised Behavior Checklist
QT	Interval between Q-wave and T-wave
QTcB	Heart-rate corrected QT interval
RAAPP	Rating of Aggression Against People and/or Property
RBPC	Revised Behavior Problem Checklist
RCOH	Retrospective cohort study
RCT	Randomized Controlled Trial
R-CTRS	Conners Teacher Rating Scale, Revised
RPQ	Reactive-Proactive Aggression Questionnaire
R-TRPA	Reactive and Proactive Rating Scale, Teacher Revised
SAMHSA	Substance Abuse and Mental Health Services Administration
SCIP	Social Cognitive Intervention Program
SCL-90	Symptom Checklist, 90-item
SD	Standard Deviation
SDQ	Strengths and Difficulties Questionnaire
SESBI	Sutter-Eyberg Student Behavior Inventory
SET-PC	Supportive Expressive Therapy-Parent Child
SGA	Second-generation Antipsychotics
SIP	Scientific Information Packets
SKAMP	Swanson Kotkin Atkins M-Flynn and Pelham Scale
SNAP-IV	Swanson Nolan and Pelham-IV
SNAP ORP	Stop Now and Plan Under 12 Outreach Project
SOE	Strength of Evidence
SRC	Scientific Resource Center
SRD	Self-report Delinquency Scale
SRDR	Systematic Review Data Repository
SSQ	School Situations Questionnaire
SSRI	Selective Serotonin Reuptake Inhibitors
SSS	Sensation Seeking Scale
SST	Social Skills Training
STAXI	State-Trait Anger and Expression of Anger Inventory
SUDD	Substance Use Disorder Diagnosis Schedule
TAU	Treatment As Usual
TCIT	Teacher-Child Interaction Training
T-MAY	Treatment of Maladaptive Aggression in Youth
TPA	Top Problems Assessment
TRAAY	Treatment Recommendations for the use of Antipsychotics for Aggressive Youth

TRF	Teacher Report Form
Triple P	Positive Parenting Program
VAQ	Vitiello Aggression Questionnaire
VAS-TO	Visual Analogue Scale of Target Outcome
VPA	Valproic Acid
WLC	Waitlist Control
YOT	Youth Offending Team
YSR	Youth Self Report
XR	Extended release

Appendix A. Search Strategies

Table A-1. MEDLINE search strategies updated (PubMed interface) December 11, 2013

Search terms		Results
Psychosocial interventions		
#1	attention deficit and disruptive behavior disorders[mh:noexp] OR conduct disorder[mh] OR (mental disorders[mh] AND aggression[mh]) OR externalizing behavior*[tiab] OR externalizing behaviour*[tiab] OR oppositional defian*[tiab] OR conduct disorder*[tiab] OR disruptive behavior disorder*[tiab] OR antisocial personality disorder[mh] OR conduct problems[tiab] OR antisocial behavior*[tiab]	23579
#2	therapy[sh] OR therapeutics[mh] OR teaching[mh] OR psychotherapy[mh] OR treatment outcome[mh] OR "Adolescent Transitions Program"[tiab] OR "Anger control training"[tiab] OR "Assertive training"[tiab] OR "Behavioral parent training"[tiab] OR "Brief Strategic Family Therapy"[tiab] OR "Collaborative Problem Solving"[tiab] OR "Coping Power"[tiab] OR "Early Risers Skills for Success"[tiab] OR "Skills for Success Program"[tiab] OR "First Step to Success"[tiab] OR "Functional Family Therapy"[tiab] OR "Helping the Noncompliant Child"[tiab] OR "Incredible Years"[tiab] OR "Interpersonal skills training"[tiab] OR "Multidimensional Family Therapy"[tiab] OR "Multidimensional Treatment Foster Care"[tiab] OR "Multisystemic Therapy"[tiab] OR "Multi-systemic Therapy"[tiab] OR "Parent Management Training"[tiab] OR "Parent-Child Interaction Therapy"[tiab] OR "Positive Parenting Program"[tiab] OR "Problem Solving Skills Training"[tiab] OR "Positive Behavioral Support System"[tiab] OR "Promoting Alternative Thinking Strategies"[tiab] OR "Second Step"[tiab] OR "Self-Control training"[tiab] OR "Teacher-Child Interaction Training"[tiab] OR "Teacher Child Interaction Training"[tiab]	6753849
#3	eng[la] AND (child[mh] OR adolescent[mh])	1775464
#4	newspaper article[pt] OR letter[pt] OR comment[pt] OR case reports[pt] OR review[pt] OR practice guideline[pt] OR news[pt] OR editorial[pt] OR historical article[pt] OR meta-analysis[pt] OR legal cases[pt] OR published erratum[pt] OR congresses[pt] OR jsubsetk	4996769
#5	(#1 AND #2 AND #3) NOT #4	3181
#6	(oppositional defian*[tiab] OR conduct disorder*[tiab] OR disruptive behavior disorder*[tiab] OR disruptive behaviour disorder*[tiab] OR conduct problem*[tiab] OR antisocial behavior*[tiab] OR antisocial behavior*[tiab] OR ((externaliz*[tiab] OR aggressi*[tiab]) AND (behavior*[tiab] OR behaviour*))) NOT medline[sb]	3745
#7	(therapy[tiab] OR effectiveness[tiab] OR efficacy[tiab] OR outcome[tiab] OR treatment*[tiab] OR randomized[tiab] OR "Adolescent Transitions Program"[tiab] OR "Anger control training"[tiab] OR "Assertive training"[tiab] OR "Behavioral parent training"[tiab] OR "Brief Strategic Family Therapy"[tiab] OR "Collaborative Problem Solving"[tiab] OR "Coping Power"[tiab] OR "Early Risers Skills for Success"[tiab] OR "Skills for Success Program"[tiab] OR "First Step to Success"[tiab] OR "Functional Family Therapy"[tiab] OR "Helping the Noncompliant Child"[tiab] OR "Incredible Years"[tiab] OR "Interpersonal skills training"[tiab] OR "Multidimensional Family Therapy"[tiab] OR "Multidimensional Treatment Foster Care"[tiab] OR "Multisystemic Therapy"[tiab] OR "Multi-systemic Therapy"[tiab] OR "Parent Management Training"[tiab] OR "Parent-Child Interaction Therapy"[tiab] OR "Positive Parenting Program"[tiab] OR "Problem Solving Skills Training"[tiab] OR "Positive Behavioral Support System"[tiab] OR "Promoting Alternative Thinking Strategies"[tiab] OR "Second Step"[tiab] OR "Self-Control training"[tiab] OR "Teacher-Child Interaction Training"[tiab] OR "Teacher Child Interaction Training"[tiab]) NOT medline[sb]	388791
#8	(child*[tiab] OR youth*[tiab] OR adolescen*[tiab] OR teen*[tiab] OR preschool*[tiab] OR parent*[tiab] OR family[tiab] OR families[tiab] OR juvenile*[tiab] OR school-age*[tiab]) NOT medline[sb]	149580
#9	#6 AND #7 AND #8	564
#10	#5 OR #9 (Medline and non-indexed results)	3745
Pharmacologic interventions		
#11	attention deficit and disruptive behavior disorders[mh:noexp] OR conduct disorder[mh] OR (mental disorders[mh] AND aggression[mh]) OR externalizing behavior*[tiab] OR externalizing behaviour*[tiab] OR oppositional defian*[tiab] OR conduct disorder*[tiab] OR disruptive behavior disorder*[tiab] OR antisocial personality disorder[mh] OR conduct problems[tiab] OR antisocial behavior*[tiab]	23579

Search terms		Results
#12	"drug therapy" [Subheading] OR "Drug Therapy"[Mesh] OR "Antipsychotic Agents"[Mesh] OR "Antipsychotic Agents" [Pharmacological Action] OR "Adrenergic alpha-Agonists"[Mesh] OR "Adrenergic alpha-2 Receptor Agonists"[Mesh] OR "Anticonvulsants"[Mesh] OR "Anticonvulsants" [Pharmacological Action] OR "Serotonin Uptake Inhibitors"[Mesh] OR "Serotonin Uptake Inhibitors" [Pharmacological Action] OR "Central Nervous System Stimulants"[Mesh]	2353195
#13	eng[la] AND (child[mh] OR adolescent[mh])	1775464
#14	newspaper article[pt] OR letter[pt] OR comment[pt] OR case reports[pt] OR review[pt] OR practice guideline[pt] OR news[pt] OR editorial[pt] OR historical article[pt] OR meta-analysis[pt] OR legal cases[pt] OR published erratum[pt] OR congresses[pt] OR jsubsetk	4996769
#15	(#11 AND #12 AND #13) NOT #14	685
Pharmacologic or psychosocial interventions		
#16	#15 OR #10 (all results)	3781
#17	#10 NOT #15	3096

Key: [mh] Medical Subject Heading; [tiab] title/abstract word; [pt] publication type; [sh] subheading;
*Note: numbers do not tally as some articles are excluded in more than one category
After duplicates were removed, this search contributed 1678 records to the existing 2407 in the database, for a total of 4085 records.

Table A-2. MEDLINE search strategies updated (PubMed interface) January 13, 2014

Search terms		Results
#1	"aggressive behavior"[tiab] OR "aggressive behaviors"[tiab] OR "aggressive behavior"[tiab] OR "aggressive behaviours"[tiab] OR "aggressive children"[tiab] OR "aggressive child"[tiab] OR "aggressive adolescent"[tiab] OR "aggressive adolescents"[tiab] OR "adolescent aggression"[tiab] OR "child aggression"[tiab] OR "antisocial behavior"[tiab] OR "antisocial behaviors"[tiab] OR "antisocial behaviour"[tiab] OR "antisocial behaviours"[tiab] OR "aggressive disruptive"[tiab] OR "Attention Deficit and Disruptive Behavior Disorders"[Mesh:NoExp] OR "behavior disorder"[tiab] OR "behavior disorders"[tiab] OR "behaviour disorder"[tiab] OR "behaviour disorders"[tiab] OR "conduct disorder"[tiab] OR "conduct disorders"[tiab] OR "Conduct Disorder"[mesh] OR "conduct problems"[tiab] OR "disruptive behavior"[tiab] OR "disruptive behaviour"[tiab] OR "disruptive behaviors"[tiab] OR "disruptive behaviours"[tiab] OR "externalizing disorder" OR "externalizing disorders" OR "externalizing behavior"[tiab] OR "externalizing behaviors"[tiab] OR "externalizing behaviour"[tiab] OR "externalizing behaviours"[tiab] OR "externalizing problem behavior"[tiab] OR "externalizing problem behaviors"[tiab] OR "externalizing problem behaviour"[tiab] OR "externalizing problem behaviours"[tiab] OR "oppositional defiant"[tiab] OR "oppositional defiance"[tiab] OR oppositionality[tiab] OR ((Aggression[Mesh] OR aggression[tiab] OR bullying[tiab] OR noncompliant[tiab] OR defiance[tiab] OR defiant[tiab] OR disruptive[tiab] OR oppositional[tiab] OR antisocial[tiab] OR "Psychomotor Agitation"[mesh]) AND ("Child Behavior"[mesh] OR "Adolescent Behavior"[mesh] OR behavior[tiab] OR behaviour[tiab] OR behaviors[tiab] OR behaviours[tiab] OR conduct[tiab]))	36627
#2	"anger management"[tiab] OR "anger control"[tiab] OR "behavior management"[tiab] OR "behaviour management"[tiab] OR "behavioral management"[tiab] OR "behavioural management"[tiab] OR "behavioral support"[tiab] OR "behavioural support"[tiab] OR "cognitive therapy"[tiab] OR "cognitive behavior therapy"[tiab] OR "cognitive behaviour therapy"[tiab] OR "CBT"[tiab] OR "cognitive behavioral therapy"[tiab] OR "cognitive behavioural therapy"[tiab] OR "conflict management"[tiab] OR counseling[tiab] OR "coping power"[tiab] OR "Counseling"[Mesh] OR "drug therapy"[tiab] OR "early intervention"[tiab] OR "family therapy"[tiab] OR "multisystemic therapy"[tiab] OR "multi-systemic therapy"[tiab] OR "multidimensional treatment"[tiab] OR "multidimensional therapy"[tiab] OR "nonpharmacologic therapy"[tiab] OR "nondrug therapy"[tiab] OR "non-drug therapy"[tiab] OR "parent training"[tiab] OR "parent engagement"[tiab] OR "parent management"[tiab] OR "parenting skills"[tiab] OR "parenting intervention"[tiab] OR "parenting interventions"[tiab] OR "family training"[tiab] OR "family education"[tiab] OR "family intervention"[tiab] OR "family interventions"[tiab] OR "pharmacologic therapy"[tiab] OR "pharmacologic treatment"[tiab] OR "Problem Solving"[Mesh] OR "problem solving"[tiab] OR "Psychology, Applied"[Mesh] OR psychoeducation[tiab] OR "psychosocial therapy"[tiab] OR "psychosocial intervention"[tiab] OR "psychosocial interventions"[tiab] OR "psychosocial approach"[tiab] OR "psychosocial approaches"[tiab] OR "psychosocial treatment"[tiab] OR	4613496

Search terms		Results
	"psychosocial support"[tiab] OR "Psychotherapy"[Mesh] OR psychotherap*[tiab] OR "skills training"[tiab] OR "symptom management"[tiab] OR teaching[tiab] OR "Therapeutics"[Mesh:NoExp] OR treatment[tiab] OR therapy[tiab] OR training[tiab] OR "Treatment Outcome"[Mesh] OR "Adrenergic alpha-2 Receptor Agonists" [Pharmacological Action] OR "Adrenergic alpha-2 Receptor Agonists"[Mesh] OR "alpha-2 agonist"[tiab] OR "alpha-2 agonists"[tiab] OR "Antidepressive Agents"[Mesh] OR "Antidepressive Agents" [Pharmacological Action] OR antidepressant[tiab] OR antidepressants[tiab] OR "Antipsychotic Agents"[Mesh] OR "Antipsychotic Agents" [Pharmacological Action] OR antipsychotics[tiab] OR antipsychotic[tiab] OR "mood stabilizer"[tiab] OR "mood stabilizing"[tiab] OR "mood stabilizers"[tiab] OR psychostimulant[tiab] OR psychostimulants[tiab] OR "Serotonin Uptake Inhibitors"[Mesh] OR "SSRI"[tiab] OR "SSRIs"[tiab] OR "selective serotonin reuptake inhibitors"[tiab] OR "Serotonin Uptake Inhibitors" [Pharmacological Action] OR stimulants[tiab] OR "Central Nervous System Stimulants"[Mesh] OR "Central Nervous System Stimulants" [Pharmacological Action] OR "Sympatholytics"[Mesh] OR "Sympatholytics" [Pharmacological Action] OR sympatholytic[tiab] OR sympatholytics[tiab]	
#3	#1 AND #2 AND english[la] AND (child[mh] OR adolescent[mh] OR child*[tiab] OR teen*[tiab] OR adolescent*[tiab] OR adolescence[tiab] OR pediatric[tiab] OR paediatric*[tiab])	6076
#4	newspaper article[pt] OR letter[pt] OR comment[pt] OR case reports[pt] OR review[pt] OR practice guideline[pt] OR news[pt] OR editorial[pt] OR historical article[pt] OR meta-analysis[pt] OR legal cases[pt] OR published erratum[pt] OR congresses[pt] OR jsubsetk	5028324
#5	#3 NOT #4	4695

Key: [mh] Medical Subject Heading; [tiab] title/abstract word; [pt] publication type; [sh] subheading;
*Note: numbers do not tally as some articles are excluded in more than one category
This search, less the duplicates, contributed 2716 citations for a total of 6801 records for initial screening

Table A-3. PsycINFO (via ProQuest interface) search results, November 26, 2013

Search terms		Results
PsycInfo- psychosocial		
#1	SU.EXACT("Conduct Disorder") OR SU.EXACT("Oppositional Defiant Disorder") OR SU.EXACT("Antisocial Personality Disorder") OR (disruptive behavior disorder OR disruptive behavior disorders)	11181
#2	SU.EXACT.EXPLODE("Treatment") OR SU.EXACT.EXPLODE("Medicinal Herbs and Plants") OR SU.EXACT.EXPLODE("Dietary Supplements") OR SU.EXACT.EXPLODE("Nutrition") OR SU.EXACT.EXPLODE("Vitamins") OR SU.EXACT("Drug Therapy") OR SU.EXACT.EXPLODE("Behavior Therapy")	573194
#3	#1 and #2	2580
#4	#3, limited children and adolescents	1558
#5	#3, limited to 2003-2013 publication date	1323
#6	#3 limited to peer reviewed, scholarly journals	1719
#7	#3 limited to research methodology (Empirical Study OR Quantitative Study OR Treatment Outcome/Clinical Trial OR Longitudinal Study OR Followup Study OR Retrospective Study OR Prospective Study OR Field Study)	1200
#8	#3 AND #4 AND #5 AND #6 AND #7	412
PsycInfo- pharmacologic		
#9	SU.EXACT("Conduct Disorder") OR SU.EXACT("Oppositional Defiant Disorder") OR SU.EXACT("Antisocial Personality Disorder") OR (disruptive behavior disorder OR disruptive behavior disorders)	11181
#10	(SU.EXACT.EXPLODE("Adrenergic Blocking Drugs") OR SU.EXACT.EXPLODE("Adrenergic Drugs")) OR (SU.EXACT.EXPLODE("Anticonvulsive Drugs") OR SU.EXACT.EXPLODE("Antidepressant Drugs")) OR (SU.EXACT.EXPLODE("Drug Augmentation") OR SU.EXACT.EXPLODE("Drug Therapy")) OR SU.EXACT.EXPLODE("Neuroleptic Drugs") OR antipsychotic	142032
#11	#9 AND #10	643

Search terms		Results
#12	#11, limited to children and adolescents	436
#13	#11, limited to 2003-2013	384
#14	#11, limited to peer reviewed, scholarly journals	540
#15	#11, limited to research methodology ((Empirical Study OR Quantitative Study OR Treatment Outcome/Clinical Trial OR Longitudinal Study OR Followup Study OR Retrospective Study OR Prospective Study OR Field Study)	398
#16	#11 AND #12 AND #13 AND #14 AND #15	170
PsycInfo- psychosocial and pharmacologic interventions		
#17	#8 OR #16	**425**

Table A-4. Embase search strategy (OvidSP interface, includes MEDLINE results), April 18, 2014

Search terms		Search results
#1	conduct disorder/ or behavior disorder/ or disruptive behavior/ or oppositional defiant disorder/ or aggression/ or intermittent explosive disorder/ or disruptive mood dysregulation disorder.mp	80970
#2	exp antidepressant agent/ or exp neuroleptic agent/ or exp serotonin uptake inhibitor/ or exp central stimulant agent/ or exp adrenergic receptor blocking agent/ or exp alpha 2 adrenergic receptor stimulating agent/	811935
#3	#1 AND #2	13405
#4	#3 NOT (review or conference paper or conference abstract or editorial or letter or note or short survey).pt. or case report/ or practice guideline/ or systematic review/ or meta analysis/	5115
#5	#4 limit to (human and english language and exclude medline journals and yr="1994 - Current" and (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>))	70

Key: [mh] Medical Subject Heading; [la] language; [tiab] title/abstract word; [pt] publication type; [sh] subheading

Appendix B. Literature Screening Forms

Primary Literature Abstract Screening Form

First Author, Year: _____Endnote Reference ID #: _____ Abstractor Initials: __ __ __				
Primary Inclusion/Exclusion Criteria				
X-1	1. Reports original research (i.e., not commentaries, literature reviews, or systematic reviews) *NOTE: If the publication appears relevant to the topic, consider whether it should be retained for "review for references" (see check boxes below the form). These publications will be flagged for review, but not promoted for full text screening.*	Yes	No	Cannot Determine
X-2	2. Measures the relationship between a psychosocial or pharmacologic intervention and an outcome (i.e., not a descriptive study).	Yes	No	Cannot Determine
X-3	3. Population is children (youth). *NOTE: If the intervention targets parent/caregiver, the study must report at least one child outcome.*	Yes	No	Cannot Determine
X-4	4. Population has a disruptive behavior disorder which a) meets standardized disease classification or criteria for diagnosis of a disruptive behavior disorder (includes oppositional-defiant disorder and conduct disorder); **OR** b) is characterized by maladaptive behavior(s) assessed using a standardized behavior checklist, tool or measure.	Yes	No	Cannot Determine
X-5	5. Study is conducted in a healthcare setting. *NOTE: Do not include studies conducted exclusively in the juvenile justice system or school setting; do not include systems-level, universal, or preventive interventions; do not include studies conducted exclusively in hospitalized (i.e. inpatient) participants.*	Yes	No	Cannot Determine
X-6	6. The study includes an alternate treatment or intervention for comparison to measure effectiveness. `	Yes	No	Cannot Determine
Retain for: □ Background/Discussion □ Review of references □ Harms data □ Other_____ **COMMENTS:**				

Primary Literature Full-Text Screening Form

First Author, Year: _____Endnote Reference ID #: _____ Abstractor Initials: __ __ __			
If response to item #1-6 is "No" the form is complete. Consider whether the reference should be retained for background, review of references, team review, harms, or other reason, and then submit the form to move to the next reference.			
X-1	1. Reports original research (i.e., not commentaries, literature reviews, or systematic reviews) *NOTE: If the publication appears relevant to the topic, consider whether it should be retained for "review for references" (see check boxes below the form). These publications will be flagged for review, but not promoted for full text screening.*	Yes	No
X-2	2. The study measures the relationship between a psychosocial or pharmacologic intervention and an outcome (i.e., not a descriptive study). If "Yes", check one: o Randomized controlled trial o Nonrandomized controlled trial o Prospective cohort with concurrent control group o Retrospective cohort (groups NOT defined by outcome) o Other _____	Yes	No
X-3	3. The study population is children (youth). *NOTE: If the intervention targets parent/caregiver, the study must report at least one child outcome.*	Yes	No
X-4	4. The study population has a disruptive behavior disorder which: a) meets standardized disease classification or criteria for diagnosis of a disruptive behavior disorder (includes oppositional-defiant disorder and conduct disorder); **OR** b) is characterized by maladaptive behavior(s) assessed using a standardized behavior checklist, tool or measure. If "No", target population described as children with ADHD? o Yes o No	Yes	No
X-5	5. The study is conducted in a healthcare setting. *NOTE: Do not include studies conducted exclusively in the juvenile justice system or school setting; do not include systems-level, or universal interventions; do not include studies conducted exclusively in hospitalized (i.e. inpatient) participants.*	Yes	No
X-6	6. The study includes an alternate treatment or intervention for comparison to measure effectiveness. If "Yes", check one: o Compares two or more psychosocial interventions o Compares two or more pharmacologic interventions o Compares one or more psychosocial interventions with one or more pharmacologic interventions o Compares one or more combined psychosocial and pharmacologic interventions with another intervention o Compares one or more psychosocial interventions with an inactive control (e.g., waitlist) o Compares one or more psychosocial interventions with usual care o Compares one or more pharmacologic interventions with a control (e.g., placebo, untreated) o Compares one or more combined psychosocial and pharmacologic interventions with a control	Yes	No
X-7	7. The study reports an outcome of interest for the population (youth) with disruptive behavior.	Yes	No
X-8	8. Addresses Key Question (s)	Yes	No
	In children under 18 years of age treated for disruptive behaviors: ____ (KQ1) are any psychosocial interventions more effective for improving short-term and long-term psychosocial outcomes than no treatment or other psychosocial interventions? ____ (KQ2) are alpha-agonists, anticonvulsants, beta-blockers, central nervous system stimulants, first-generation antipsychotics, second-generation (atypical) antipsychotics, and selective serotonin reuptake inhibitors more effective for improving short-term and long-term psychosocial outcomes than placebo or other pharmacologic interventions? ____ (KQ3) what is the relative effectiveness of psychosocial interventions compared with the pharmacologic interventions listed in Key Question 2 for improving short-term and long-term psychosocial outcomes? ____ (KQ4) are combined psychosocial and pharmacologic interventions more effective for improving short-term and long-term psychosocial outcomes than individual interventions? ____ (KQ5) what are the harms of treatment associated with either psychosocial or pharmacologic interventions? Do interventions intended to address disruptive behaviors and identified in Key Questions 1-4 vary in		

	effectiveness based on: ____ (KQ6a) patient characteristics, including gender, age, race/ethnic minority, family history of disruptive behavior disorders, family history of mental health disorders, history of trauma, and socioeconomic status? ____ (KQ6b) characteristics of the disorder, including specific disruptive behavior or disruptive behavior disorder (e.g., oppositional defiant disorder, conduct disorder, aggression), concomitant psychopathology (e.g., attention deficit hyperactivity disorder or substance abuse), related personality traits and symptom clusters, presence of co-morbidities, age of onset, and duration? ____ (KQ6c) treatment history of the patient? ____ (KQ6d) characteristics of the treatment, including duration, delivery, timing, and dose?		

Retain for:

□ Background/Discussion □ Review of references □ Team Review □ Harms □ Other

COMMENTS:

Existing Reviews Relevance Screening Form

First Author, Year: _____ Reference ID #: _____ Reviewer Initials: ___ ___ ___	
PICOTS	Comments
Includes appropriate **population**?	
Addresses target **interventions**?	
Includes studies with **comparators** (treatment approach to no treatment, placebo, or comparative interventions/combinations of interventions)?	
Addresses target **outcomes** (including adverse effects/harms)?	
Includes studies in target **setting**?	
Other	
Study types specified? Circle applicable: RCT, controlled trials, observational studies (retrospective/prospective cohort studies, case-control, case series), individual case studies, other:_____	
When was the literature search conducted? Specify timeframe:_____	
Recommendation:	

Appendix C. Risk of Bias Assessment Forms and Summaries

Cochrane Risk of Bias Assessment Tool

Ref ID:_____ Reviewer ___ ___ ___

Domain	Description	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Reviewer Assessment	Reviewer Comments
Selection bias ***Random sequence generation***	Described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence	Random sequence generation method should produce comparable groups	Not described in sufficient detail	**High** **Low** **Unclear**	
Selection bias ***Allocation concealment***	Described the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrollment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	Intervention allocations likely could not have been foreseen in before or during enrollment	Not described in sufficient detail	**High** **Low** **Unclear**	
Reporting bias ***Selective reporting***	Stated how the possibility of selective outcome reporting was examined by the authors and what was found	Reporting bias due to selective outcome reporting	Selective outcome reporting bias not detected	Insufficient information to permit judgment†	**High** **Low** **Unclear**	
Other bias ***Other sources of bias***	Any important concerns about bias not addressed above*	Bias due to problems not covered elsewhere in the table	No other bias detected	There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists or insufficient rationale or evidence that an identified problem will introduce bias	**High** **Low** **Unclear**	

* If particular questions/entries were pre-specified in the study's protocol, responses should be provided for each question/entry.

(continued) **Ref ID:_____ Reviewer ___ ___ ___**
Assess each main or class of outcomes for each of the following. Indicate the specific outcome.
Outcome:

Domain	Description	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Reviewer Assessment	Reviewer Comments
Performance bias ***Blinding (participants and personnel)***	Described all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	Blinding was likely effective.	Not described in sufficient detail	**High** **Low** **Unclear**	
Detection bias ***Blinding (outcome assessment)***	Described all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.	Blinding was likely effective.	Not described in sufficient detail	**High** **Low** **Unclear**	
Attrition bias ***Incomplete outcome data***	Described the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Stated whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported.	Attrition bias due to amount, nature or handling of incomplete outcome data.	Handling of incomplete outcome data was complete and unlikely to have produced bias	Insufficient reporting of attrition/exclusions to permit judgment (e.g., number randomized not stated, no reasons for missing data provided)	**High** **Low** **Unclear**	

* If particular questions/entries were pre-specified in the study's protocol, responses should be provided for each question/entry.

Criteria for Judging Risk of Bias Using the Cochrane Risk of Bias Assessment Tool*

Bias	Judgment	Criteria
RANDOM SEQUENCE GENERATION **Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.**	'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
	'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
	'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.
ALLOCATION CONCEALMENT **Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.**	'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.
	'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure.
	'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

Bias	Judgment	Criteria
SELECTIVE REPORTING **Reporting bias due to selective outcome reporting.**	'Low risk' of bias.	Any of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	'High risk' of bias.	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.
OTHER BIAS **Bias due to problems not covered elsewhere in the table.**	'Low risk' of bias.	The study appears to be free of other sources of bias.
	'High risk' of bias.	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used; or • Has been claimed to have been fraudulent; or • Had some other problem.
	'Unclear risk' of bias.	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias.
BLINDING OF PARTICIPANTS AND PERSONNEL **Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.**	'Low risk' of bias.	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	'High risk' of bias.	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgment of 'Low risk' or 'High risk'; • The study did not address this outcome.

Bias	Judgment	Criteria
BLINDING OF OUTCOME ASSESSMENT **Detection bias due to knowledge of the allocated interventions by outcome assessors.**	'Low risk' of bias.	Any one of the following: • No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	'High risk' of bias.	Any one of the following: • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but likely that the blinding could have been broken and the outcome measurement is likely to be influenced by lack of blinding.
	'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgment of 'Low risk' or 'High risk'; • The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Attrition bias due to amount, nature, or handling of incomplete outcome data.**	'Low risk' of bias.	Any one of the following: • No missing outcome data; • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • Missing data have been imputed using appropriate methods.
	'High risk' of bias.	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; • Potentially inappropriate application of simple imputation.
	'Unclear risk' of bias.	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); • The study did not address this outcome.
* Adapted from the Cochrane Collaboration		

RTI Bank Risk of Bias Assessment Form

Ref ID:_____ Reviewer ___ ___ ___

		No	Yes	Comments
Questions to Assess the Risk of Bias				
Q1	Do the inclusion/exclusion criteria vary across the comparison groups of the study?			
Q2	Does the strategy for recruiting participants into the study differ across groups?			
Q3	Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?			
Q4	Was the outcome assessor not blinded to the intervention or exposure status of participants?			
Q5	Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant health benefits and harms, and confounding?			
Q6	Was the length of followup different across study groups?			
Q7	In cases of high loss to followup (or differential loss to followup), was the impact assessed (e.g., through sensitivity analysis or other adjustment method)?			
Questions to Assess Confounding				
Q8	Any attempt to balance the allocation between the groups or match groups (e.g., through stratification, matching, propensity scores)?			
Q9	Were the important confounding variables taken into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?			
Questions to Assess Precision				
Q10	Are the statistical methods used to assess the primary benefit outcomes inadequate?			
Q11	Are the statistical methods used to assess the main harm or adverse event outcomes inadequate?			

Based on cohort questions from: Viswanathan M, Berkman ND, Dryden DM, et al. Assessing Risk of Bias and Confounding in Observational Studies of Interventions or Exposures: Further Development of the RTI Item Bank [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Aug. Available from: http://www.ncbi.nlm.nih.gov/books/NBK154461/

Risk of Bias Assessment Form: Harms Reporting

Reviewer: _____ Ref ID: _____			
Question	**Yes**	**No**	**Comments**
Were the harms predefined using standardized or precise definitions? (McHarms)			
Are all pre-specified harms reported? (RTI case series)			
Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection? (McHarms)			
Are the statistical methods used to assess the main harm or adverse event outcomes adequate? (RTI cohort)			

Quality Assessment Form (AMSTAR): Systematic Reviews

1. Was *a priori* design provided?	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction?	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed?	□ Yes □ No □ Can't answer □ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	□ Yes □ No □ Can't answer □ Not applicable
5. Was a list of studies (included and excluded) provided?	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided?	□ Yes □ No □ Can't answer □ Not applicable
7. Was the scientific quality of the included studies assessed and documented?	□ Yes □ No □ Can't answer □ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	□ Yes □ No □ Can't answer □ Not applicable
9. Were the methods used to combine the findings of studies appropriate?	□ Yes □ No □ Can't answer □ Not applicable
10. Was the likelihood of publication bias assessed?	□ Yes □ No □ Can't answer □ Not applicable
11. Was the conflict of interest included?	□ Yes □ No □ Can't answer □ Not applicable

Adapted from: Shea BJ et al., BMC Medical Research Methodology 2007

Assessment of Overall Risk of Bias for Individual Studies

There are three categories for describing the overall risk of bias for assessed studies: low risk of bias; moderate risk of bias; and high risk of bias.

Cochrane Risk of Bias Assessment Tool

Use for risk of bias assessments for ***randomized controlled trials (RCTs)***.

The tool includes seven items in six domains:

- Selection Bias *(2 items)*
- Reporting bias *(1 item)*
- Other bias *(1 item)*
- Performance bias *(1 item)*
- Detection bias *(1 item)*
- Attrition bias *(1 item)*

The overall risk of bias for an RCT is calculated from individual domain assessments:

- **Low**: "low" for all domains.
- **Moderate**: "unclear" for one or more domains and no known important limitation that could invalidate its results.
- **High**: "high" for one or more domains.

RTI Bank Risk of Bias Assessment Form

Use for risk of bias assessments for ***cohort/non-randomized controlled studies***.

The form includes eleven items in three domains:

- Risk of Bias *(7 items)*
- Confounding *(2 items)*
- Precision *(2 items)*

The overall risk of bias for a cohort/non-randomized controlled study is calculated from individual domain assessments:

- **Low**: all "positive"
- **Moderate**: two or fewer "negative"
- **High**: more than two "negative"

Table C-1. Risk of bias assessment summary for KQ1 RCTs

Citation	AgeCat	Random Sequence Generation	Allocation Conceal	Selective Reporting	Other Bias	Outcome(s)	Blinding (pts, personnel)	Blinding (outcome assess)	Incomplete Outcome Data	Low	High	Unclear	Overall Score
Perrin et al., 2013[1]	PRE-K	L	U	L	U	ECBI	H	H	L	3	2	2	Moderate
Jones, et al., 2013[2]	PRE-K	U	U	L	L	ECBI problem, ECBI intensity	U	U	H	2	1	4	High
Somech et al., 2012[3]	PRE-K	L	U	U	L	ECBI Intensity	U	U	L	3	0	4	Moderate
Cummings et al., 2008[4]	PRE-K	L	L	U	H	CBCL,ECBI	H	H	H	2	4	1	High
Lavigne, et al., 2008[5]	PRE-K	U	U	U	H	ECBI, CBCL	U	U	U	0	1	6	High
Hutchings et al., 2007[6]	PRE-K	L	L	L	L	ECBI	H	L	L	6	1	0	Moderate
Markie-Dadds, et al., 2006[7]	PRE-K	U	U	U	U	ECBI Intensity, ECBI Problem, PDR	U	U	L	1	0	6	Moderate
McGilloway, et al., 2012[8]	PRE-K	L	L	U	H	ECBI	L	L	L	5	1	1	Low
Markie-Dadds, et al., 2006[9]	PRE-K	L	U	U	U	ECBI Intensity, ECBI Problem, PDR	H	H	H	1	3	3	Moderate
Sanders et al., 2000[10]	PRE-K	U	U	U	L	ECBI, PDR, PS, PSOC, ADAS, PPC, PASS	H	H	H	1	3	3	Moderate
Connell, et al., 1997[11]	PRE-K	L	U	U	U	ECBI (intensity), ECBI (problem), PDRC	H	U	L	2	1	4	High
Sanders, et al., 2012[12]	PRE-K	L	u	U	H	ECBI intensity, ECBI problem, SDQ	H	U	L	2	2	3	High
Jouriles, et al., 2001[13]	PRE-K	U	U	U	H	CBCL, direct observation	U	U	U	0	1	6	High
Bagner, et al., 2010[14]	PRE-K	L	U	U	L	CBCL (externalizing), CBCL (aggression), ECBI (intensity), ECBI (problem)	H	H	H	2	3	2	High

Citation	AgeCat	Random Sequence Generation	Allocation Conceal	Selective Reporting	Other Bias	Outcome(s)	Blinding (pts, personnel)	Blinding (outcome assess)	Incomplete Outcome Data	Low	High	Unclear	Overall Score
McCabe, et al., 2009[15]	PRE-K	L	U	U	L	ECBI, CBCL, ARSMA-II	L	L	L	5	0	2	Low
Schuhmann et al., 1998[16]	PRE-K	L	L	U	L	DPICS	U	L	H	4	1	2	Moderate
Eyberg et al., 1995[17]	PRE-K	U	U	U	L	ECBI intensity, ECBI problem	H	U	H	1	2	4	High
Nixon, et al., 2003[18]	PRE-K	U	U	U	L	ECBI Intensity, DPICS	U	H	L	2	1	4	Moderate
Sells, et al., 2011[19]	PRE-K	U	U	U	U		H	H	L	1	2	4	Moderate
Sanders, et al., 2000[20]	PRE-K	U	U	U	U		H	H	U	0	2	5	High
Havighurst, et al., 2013[21]	PRE-K	L	L	U	L		H	H	U	3	2	2	Moderate
Nixon, et al., 2001[22]	PRE-K	U	U	U	U		H	H	U	0	2	5	High
van Manen et al., 2004[23]	SCHOOL	U	L	U	U	CBCL, TOPS, TRA, SCRS, SCST	U	U	H	1	1	5	Moderate
Kjobli, et al., 2012[24]	SCHOOL	L	U	U	U	ECBI, CBCL	H	H	L	2	2	3	High
Axberg, et al., 2012[25]	SCHOOL	U	U	U	H	ECBI	H	H	L	1	3	3	High
McGrath, et al., 2011[26]	SCHOOL	L	L	L	L	K-SADS	U	L	L	6	0	1	Low
Kling, et al., 2010[27]	SCHOOL	U	U	U	L	PDR, ECB1, ECBIP	U	U	L	2	0	5	Moderate
Ogden et al., 2008[28]	SCHOOL	L	L	U	L	CBCL, SSRS, PDR	U	U	L	4	0	3	Moderate
Gardner, et al., 2006[29]	SCHOOL	L	L	U	U	ECBI	U	U	L	3	0	4	Moderate
Webster-Stratton et al., 1994[30]	SCHOOL	U	U	U	L	CBCL, ECBI, DPICS	U	U	U	1	0	6	Moderate
Hutchings, et al., 2002[31]	SCHOOL	U	U	U	U	ECBI	U	U	L	1	0	6	Moderate
Scott et al., 2010[32]	SCHOOL	L	L	L	U	PACS, ECBI	L	L	L	6	0	1	Low

Citation	AgeCat	Random Sequence Generation	Allocation Conceal	Selective Reporting	Other Bias	Outcome(s)	Blinding (pts, personnel)	Blinding (outcome assess)	Incomplete Outcome Data	Low	High	Unclear	Overall Score
Larsson, et al., 2009[33]	SCHOOL	U	U	U	L	ECBI, CBCL, KSADS-PL	U	U	L	2	0	5	Moderate
van de Wiel et al., 2007[34]	SCHOOL	U	U	U	U	CBCL, CBCL,TRF	U	U	L	1	0	6	Moderate
Drugli, et al., 2006[35]	SCHOOL	U	U	U	H	ECBI, CBCL, KSANS	H	H	L	1	3	3	Moderate
Webster-Stratton et al., 2004[36]	SCHOOL	U	U	U	L	ECBI, CBCL	U	U	U	1	0	6	Moderate
Cabiya et al., 2008[37]	SCHOOL	U	U	U	H	BSBI, CDI	U	L	H	1	2	4	High
Webster-Stratton et al., 1997[38]	SCHOOL	U	U	U	L	CBCL,EBCI Intensity, PDR	U	U	L	2	0	5	Moderate
Boylan, et al., 2013[39]	SCHOOL	U	U	U	U	ChIPS, P-ChIPS, CDRS-R, MRS, MSI	U	L	L	2	0	5	Moderate
Augimeri et al., 2007[40]	SCHOOL	U	U	U	H	CBCL	U	U	L	1	1	5	Moderate
Kolko, et al., 2001[41]	SCHOOL	L	U	U	L	FHS, CP w, fire, CFI, SUFA	U	U	L	3	0	4	Moderate
Kolko, et al., 2010[42]	SCHOOL	L	U	U	L	PSC-17; SDQ	U	H	L	3	1	3	Moderate
Kolko, et al., 2009[43]	SCHOOL	L	U	U	L	KSADS, TRE, CBCL	U	U	L	3	0	4	Moderate
Greene, et al., 2004[44]	SCHOOL	U	U	U	U	PCRI, PSI.ODBRS, C6I, KSADS-E	U	U	L	1	0	6	Moderate
Jouriles, et al., 2009[45]	SCHOOL	L	H	U	L	CBCL-EXT, ECBI	H	H	U	2	3	2	High
Barrett, et al., 2000[46]	SCHOOL	U	U	U	U		H	H	U	0	2	5	High
Brestan, et al., 1997[47]	SCHOOL	U	U	U	L		H	H	L	2	2	3	Moderate
Rohde et al., 2004[48]	TEEN	L	L	H	H	Conduct Disorder, BDI-II, HDRS, CBCL, CGAS, SAS-R	L	L	U	4	2	1	High
Weiss et al., 2013[49]	TEEN	U	U	U	L	CBCL	U	U	L	2	0	5	Moderate
Butler, et al., 2011[50]	TEEN	L	L	U	L	arrest records	U	L	L	5	0	2	Low

Citation	AgeCat	Random Sequence Generation	Allocation Conceal	Selective Reporting	Other Bias	Outcome(s)	Blinding (pts, personnel)	Blinding (outcome assess)	Incomplete Outcome Data	Low	High	Unclear	Overall Score
Asscher et al., 2013[51]	TEEN	L	U	L	U	CBCL - parents + YSR	U	H	L	3	1	3	High
Borduin et al., 1995[52]	TEEN	L	U	U	U	symptom checklist, RPBX, FACES II	U	U	H	1	1	5	Moderate
Sundell et al., 2008[53]	TEEN	L	L	L	L	CBCL	U	U	L	5	0	2	Low
Shechtman, et al., 2006[54]	TEEN	U	U	U	U	CBCL, CCNES	U	U	L	1	0	6	Moderate
Santisteban et al., 2003[55]	TEEN	U	U	U	L	RBPC	U	U	H	1	1	5	High
Nickel, et al., 2006[56]	TEEN	L	L	L	L	ARBS, STAXI, SF-36	L	L	L	7	0	0	Low
Nickel, et al., 2005[57]	TEEN	L	L	L	L	ARBS, STAXI	L	L	L	7	0	0	Low
Nickel, et al., 2006[58]	TEEN	L	L	U	U	Salivary, STAXI	U	L	L	4	0	3	Moderate
Azrin, et al., 2001[59]	TEEN	H	U	U	L		H	L	H	2	3	2	High

Table C-2. Risk of bias assessment summary for KQ1 cohort/nonrandomized controlled studies

Author, Year	Inclusion/exclusion criteria across groups	Recruitment strategy across groups	Selection of the comparison group	Outcome assessor blinding	Valid & reliable measures across study participants	Length of followup different across groups	Assessment of impact of high loss to followup	Balancing allocation between groups/matching groups	Accounting for confounding factors	Adequacy of statistical methods to assess primary outcomes	Adequacy of statistical methods to assess harms or adverse events outcomes	Rating
van der Put et al., 2013[60]	+	+	-	-	-	-	NA	-	-	+	NA	Poor
Koegl et al., 2008[61]	+	-	+	-	+	+	-	+	+	+	NA	Poor
Posthumus et al., 2012[62]	+	+	+	-	+	+	NA	+	+	+	NA	Fair
Lipman et al., 2008[63]	+	+	+	-	+	+	-	-	+	+	NA	Poor
Costin et al., 2004[64]	+	+	+	-	+	+	-	-	-	-	NA	Poor
Coughlin 2009[65]	+	+	+	-	+	+	-	-	-	+	NA	Poor
Shapiro et al., 2012[66]	+	+	+	-	+	-	+	-	+	+	NA	Poor
Foster et al, 2007[67]	+	+	+	-	+	-	-	NA	-	+	NA	Poor
Masi et al., 2014[68]	+	+	+	-	+	+	NA	+	+	+	NA	Fair

Table C-3. Risk of bias assessment summary for KQ2 RCTs

Citation (Family)	Drug	Random Sequence Generation	Allocation Conceal	Selective Reporting	Other Bias	Outcome(s)	Blinding (pts/ personnel)	Blinding (outcome assess)	Incomplete Outcome Data	Low	High	Unclear	Overall Score
Dittmann et al., 2011[69]	Atomoxetine	L	L	U	L	ECBI, SNAP	U	U	H	3	1	3	Moderate
Connor et al., 2010[70]	Guanfacine	L	L	L	L	CPRS	U	U	L	5	0	2	Moderate
Saxena et al., 2010[71]	Divalproex	H	U	L	H	CGI; OAS	H	H	H	1	5	1	High
Blader et al., 2009[72]	Divalproex	L	U	L	U	OAS	U	H	L	3	2	2	Moderate
Dell'Agnello et al., 2009[73]	Atomoxetine	U	U	L	L	SWAR-IV, CGI-S, CPRS-S	U	U	L	3	0	4	High
Connor et al., 2008[74]	Quetiapine	U	U	L	U	CGI-S; OAS; CPRS-CP	L	L	L	4	1	2	Moderate
Armenteros et al., 2007[75]	Risperidone	U	U	L	U	CAS; CGI	L	L	L	4	1	2	Moderate
Spencer et al., 2006[76]	Amphetamine	U	U	L	L	SNAP	U	U	L	3	0	4	High
Reyes et al., 2006[77]	Risperidone	U	U	L	U	CGI; CGAS	U	U	H	1	2	4	High
Steiner et al., 2003[78]	Divalproex	U	U	L	U	CGI	U	L	L	3	1	3	Moderate
Donovan et al., 2000[79]	Divalproex	U	U	L	L	OAS	L	L	L	3	0	4	Moderate
Findling et al., 2000[80]	Risperidone	L	L	L	U	CBCL; CPRS	L	L	L	6	0	1	Low
Klein et al., 1997[81]	Methylphenidate	H	H	L	U	CTRS; IOWA	H	H	L	2	4	1	High

Table C-4. Risk of bias assessment summary for KQ2 cohort/nonrandomized controlled studies

Author, Year	Inclusion/exclusion criteria across groups	Recruitment strategy across groups	Selection of the comparison group	Outcome assessor blinding	Valid & reliable measures across study participants	Length of followup different across groups	Assessment of impact of high loss to followup	Balancing allocation between groups/matching groups	Accounting for confounding factors	Adequacy of statistical methods to assess primary outcomes	Adequacy of statistical methods to assess harms or adverse events outcomes	Rating
Bastiaens et al., 2009[82]	+	+	+	-	+	+	+	-	-	-	-	Poor

Table C-5. Risk of bias assessment summary for KQ5 studies reporting harms

Author, Year	Were the harms predefined using standardized or precise definitions?	Were all pre-specified harms reported?	Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?	Were the statistical methods used to assess the main harm adequate?	Rating
Dittmann et al., 2011[69]	+	Unsure	-	-	Poor
Dell'Agnello et al., 2009[73]	-	Unsure	-	+	Poor
Connor et al., 2010[70]	+	Unsure	Unsure	+	Poor
Bastiaens et al., 2009[82]	-	Unsure	+	+	Poor
Connor et al., 2008[74]	+	+	+	+	Good
Spencer et al., 2006[76] and Connor et al., 2005[83]	-	Unsure	Unsure	+	Poor
Steiner et al., 2003[78]	-	Unsure	Unsure	-	Poor
Donovan et al., 2000[79]	-	Unsure	Unsure	+	Poor
Blader et al., 2009[72]	+	Unsure	+	+	Fair
Ercan et al., 2003[84]	+	+	-	+	Fair
Armenteros et al., 2007[75]	+	+	+	+	Good
Penzner et al., 2009[85]	+	+	+	+	Good
Reyes et al., 2006[77] and Pandina et al., 2009[86]	-	Unsure	+	+	Fair
Findling et al., 2000[80]	+	+	+	+	Good
Klein et al., 1997[81]	-	Unsure	-	-	Poor

Table C-6. Summary of quality assessment for KQ5 existing reviews reporting harms

Author, Year	A priori design	Duplicate study selection/ extraction	Comprehensive literature search	Status of publication as exclusion criterion	Included and excluded studies provided	Characteristics of included studies provided	Quality assessed	Quality used appropriately	Synthesis methods appropriate	Publication bias assessed	Conflict of interest stated	Rating
Loy et al., 2012[87]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Good
Seida et al., 2012[88]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Pringsheim et al., 2011[89]	Yes	Yes	No	Yes	No	yes	Yes	Yes	Yes	No	Yes	Good

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Appendix D. Meta-Analytic Methods

We developed a meta-analysis to address Key Question 1, which concerns the comparative effectiveness of psychosocial interventions for improving psychosocial outcomes for children treated for disruptive behaviors. We employed a Bayesian multivariate, mixed treatment (network) meta-analytic methods[1-3] to use both direct and indirect evidence for comparing a large suite of treatments.

Of the 16 instruments used to measure treatment outcomes, we included studies that employed one or more of the four most prevalent instruments: 1) Eyberg Child Behavior Inventory (ECBI), Intensity Subscale; 2) ECBI, Problem Scale; 3) Child Behavior Checklist (CBCL), Externalizing (T-score); 4) CBCL, Externalizing (raw score). Studies were included in the meta-analysis if they reported baseline and end-of-treatment (EOT) means and standard deviations from one of the four metrics listed above. In total, 28 studies were used to fit the model. The baseline was subtracted from the EOT mean and used as the response measure.

Equation 1. Response measure equals end of treatment mean minus the baseline mean

$$d_i = y_i^{(eot)} - y_i^{(bl)}$$

The response expected values m were modeled jointly as a multivariate normal likelihood, with any unmeasured outcomes treated as missing data; this allowed for the covariance among measures to be accounted for and estimated.

Equation 2. Expected value response modeled jointly as multivariate normal distribution

$$\begin{pmatrix} m_1 \\ m_2 \\ m_3 \\ m_4 \end{pmatrix}_i \sim \mathrm{MVN}(\mu, \Sigma)$$

To accommodate the large suite of interventions employed by the constituent studies, we classified each intervention according to the treatment components that comprised them. Specifically, the treatment arms of each study were classified as one of the following types: 1) child-only treatment; 2) parent-only treatment; or 3) multicomponent treatment. Thus, a given treatment arm was specified by a vector of indicator variables.

Equation 3. Treatment arm, X, specified by a vector of indicator variables, child-only, parent-only, and multicomponent

$$X_i = \begin{bmatrix} x_c \\ x_p \\ x_f \end{bmatrix}_i$$

Those not identified by any of these three classes were considered either control or treatment-as-usual arms, encoded by a zero vector. Recognizing that these treatment categories are broad,

encompassing a range of specific interventions, each component was modeled as a random effect.

Equation 4. Child-only treatment category modeled as a Gaussian random effect

$$\beta_J^{(c)} \sim N(\mu_\beta^{(c)}, \tau_\beta^{(c)})$$

Equation 5. Parent-only treatment category modeled as a Gaussian random effect

$$\beta_J^{(p)} \sim N(\mu_\beta^{(p)}, \tau_\beta^{(p)})$$

Equation 6. Multicomponent treatment category modeled as a Gaussian random effect

$$\beta_J^{(f)} \sim N(\mu_\beta^{(f)}, \tau_\beta^{(f)})$$

This allowed for variation in treatment effect within each class, due to factors not explicitly modeled here. All measurement instruments shared the same study arm treatment effect in our model, but the effect was scaled by the standard deviation of the outcome variable.

The age of subjects in each study arm was included in the model as a categorical covariate, broadly grouped into pre-kindergarten, school age, or teenage categories. The school age child was used as the baseline value because it was the most prevalent among studies. The age covariate was combined additively with the intervention component effects and control/treatment-as-usual means to model the observed treatment differences relative to baseline. Though we considered age-by-treatment interactions, there was not enough balance among the age and treatment combinations to include them in the final model. We also considered including the study age distribution as a covariate, but this was ultimately left out of the final model based on poor deviance information criterion (DIC) scores.

Outcome means, treatment effects, and the age covariate were combined to calculate expected response (treatment difference) in an additive linear model.

Equation 7. Expected responses calculated from additive linear model of outcome mean, treatment effect, and age covariate

$$\theta_i = m_{j(i)k} + X_i\beta + \alpha x_{age}$$

The likelihood of the observed differences was specified as a Gaussian distribution, with the observed standard error of the treatment effect (the sum of the baseline and EOT standard deviations) as the standard deviation of the estimates.

Equation 8. Likelihood of observed differences, specified as a Gaussian distribution, and standard deviation of estimate derived from the standard error of the treatment effect

$$d_i \sim N(\theta_i, \sigma^2)$$

All unknown parameters were given weakly-informative prior distributions and estimated using Markov chain Monte Carlo[4] methods via the PyMC 2.3 software package.[5] The model was run for 200,000 iterations, with the first 150,000 samples conservatively discarded as burn-in, leaving 50,000 for inference.

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Appendix E. Outcome Measures Used in the Meta-Analysis of Intervention Effects

The Bayesian multivariate, mixed treatment (network) meta-analysis used data from a subset of RCTs identified as addressing KQ1 that measured parent-reported child disruptive behavior using one of the following outcome measures: 1) ECBI Intensity subscale; 2) ECBI Problem subscale; 3) CBCL externalizing subscale reported as a T-score. These three measures were the most prevalent in the literature.

The Eyberg Child Behavior Inventory (ECBI)[1,2] is an inventory used in the assessment of disruptive behaviors in children ages 2 through 16 that occur in the home and in school. The ECBI is completed by parents and assesses behaviors on two scales: an Intensity Scale, which indicates how often the behaviors occur, and a Problem Scale, which identifies the specific behaviors that are cause problems for the parent. The Intensity Scale uses a frequency of occurrence rating: from *Never* (1) to *Always* (7). The sum of the Intensity Scale item ratings ranges from 36 to 252. The Problem Scale consists of a "Yes" or "No" problem identification rating for each item. The count of the "Yes" responses yields a problem score with a range from 0 to 36. The clinical cutoffs are 127 and 11 on the Intensity and Problem scales, respectively.

The Child Behavior Checklist (CBCL)[3] is part of the Achenbach System of Empirically Based Assessments (ASEBA). The target population for the CBCL is children between the ages of 6 and 18. The pre-2001 version was intended for children ages 4 to 18 years. A version of the CBCL is also available for children ages 1 ½ to 5 years of age. The CBCL obtains reports from parents, other close relatives, and/or guardians regarding children's competencies and behavioral/emotional problems. Parents provide information for 20 competence items covering their child's activities, social relations, and school performance. The CBCL/6-18 has 118 items that describe specific behavioral and emotional problems, plus two open-ended items for reporting additional problems. Parents rate their child for how true each item is now or within the past 6 months using the following scale: 0 = not true (as far as you know); 1 = somewhat or sometimes true; 2 = very true or often true. Responses to items are aggregated to generate a total score, externalizing subscale score, internalizing subscale score, empirically based syndrome scales, and/or DSM-oriented scales.

References for Appendix E

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Appendix F. Summary of Existing Systematic Reviews

Table F-1. Existing reviews of psychosocial interventions for DBD

Author, Year	Focus Area	Inclusion Criteria	Outcome(s)	# Studies Included	Key Findings
Dretzke, J., et al. (2009)[1]	Group based parent training programs	• Children with a conduct problems • Aged younger than 18 years	• Child behavior using a standardized measure	57 RCTs	• Parent and independent reports were significantly better for intervention groups • Insufficient evidence for relative effectiveness of different approaches to delivering parenting programs.
Littell, J. H., et al. (2005)[2]	Multisystemic Therapy (MST)	• Literature from 1985 to January 2003 • Children with social, emotional, and/or behavioral problems • Aged 10 to 17 years	• Crime and delinquency • Child behavior and psychosocial outcomes	8 studies	• ITT analysis found no significant differences between MST and usual services in arrests or convictions • Inconclusive evidence of the effectiveness of MST compared with other interventions with youth
Comer, J.S., et al. (2013)[3]	Psychosocial treatment	• RCTs • Children with DBD • Aged younger than 8 years at baseline	• Pooled analyses • General externalizing symptoms • Overall disruptive behavior symptoms	36 controlled trials 3,042 children	• Largest effect sizes associated with behavioral treatment, older and male youth. • Effects largest for general externalizing problems and weakest for impulsivity and hyperactivity.
McCart, M. R., et al. (2006)[4]	Behavioral parent-training (BPT) and cognitive-behavioral therapy (CBT)	• Youth with antisocial behavior problems	• Youth demographic variables were examined as potential moderators of the effectiveness	76 studies Of these, 71 were included in analyses: 30 BPT studies and 41 CBT studies	• Child age moderated outcome • BPT had a stronger effect for preschool and school-aged youth and CBT had a stronger effect for adolescents
Dretzke, J., et al. (2005)[5]	Parent training programs	• Children with conduct disorder • Aged younger than 18 years	• Clinical effectiveness • Cost-effectiveness	37 RCTs	• Six included studies were assessed as good or adequate quality • Many (n=31) of the studies that met the review inclusion and exclusion criteria were assessed as being of poor methodological quality.
Fossum, S., et al.	Psychotherapy	• 1987-2008	• Aggressive behaviors	65 studies (4,971	• Effect sizes were larger in

Author, Year	Focus Area	Inclusion Criteria	Outcome(s)	# Studies Included	Key Findings
(2008)[6]		•		patients) ; Of these 33 studies compared a psychosocial intervention with an untreated comparison group	studies of behavioral interventions compared to studies of family therapeutic interventions.
Ozabaci, N. (2011)[7]	Cognitive behavioural therapy (CBT)	• Children and adolescents demonstrating high levels of violence • 1997-2009	• Aggressive behavior	6 studies	• CBT reduced violence
Eyberg, S. M., et al. (2008)[8] update of Brestan and Eyberg, 1998	Psychosocial treatments	• Literature from 1996 to 2007 • Child and adolescent disruptive behavior, including oppositional defiant disorder and conduct disorder	• Child and adolescent disruptive behavior	16 EBTs identified (up from 12 in the earlier report)	• Studies were evaluated using criteria for EBTs developed by the task force on promotion and dissemination of psychological procedures
Bradley, M. C. and D. Mandell (2005)[9]	Interventions for ODD	• Children diagnosed with ODD	• Outcomes in 6 domains	7 studies	• Greatest effects on child behavior when interventions targeted parents • Smaller effects if only children were targeted
Johnson, M.H., et al., (2013)[10]	Behavioral interventions implemented in the community	• Children or adolescents with problem behaviors or at elevated risk	• Changes in externalizing behavior • Inattention symptoms • Social and organization skills	12 RCTs (4 family-centered behavioral intervention studies; 3 school-based behavioral intervention studies; and 5 integrated behavioral intervention studies)	• Rated level of evidence as high for behavioral management
Michelson, D., et al. (2013)[11]	Parent management training (PMT) including IY and Triple P and others	• RCTs • Studies of children consistent with guidelines on recommended target population for PMT	• Disruptive behavior problems (using a standardized outcome measure) • Child disruptive behavior across different settings	28 RCTs 2239 participants	• Significant overall advantage for PMT compared with waitlist control conditions. • No significant differences in effect size estimates according to setting • Six studies assessed as low or moderate risk of bias
Shelleby , E.C., et al. (2014)[12]	Individual or group parent training	• Children with conduct	• Moderators of	6 studies assessing baseline child	• Majority of studies on

Author, Year	Focus Area	Inclusion Criteria	Outcome(s)	# Studies Included	Key Findings
		problems • Studies that examined moderators of parenting intervention effectiveness	effectiveness including baseline level of problem behavior, sociodemographic and family process risks	behavior as a moderator 13 studies examining the mediating effect of sociodemographic and family process risks	sociodemographic and family process risks found nonsignificant association with differential intervention effectiveness • Studies of child baseline behavior suggest that increased problem behaviors at baseline are associated with increased benefit from interventions.
Piquero, A. R., et al. (2009)[13]	Parent training or support	• RCT • Children under 5 years	• Antisocial behavior • Delinquency • Parent, teacher, direct observation of child problem behavior	55 studies	• early family/parent training was effective for antisocial behavior and delinquency,
Maughan, D. R., et al. (2005)[14]	Behavioral Parent Training (BPT)	• 1966-2001 • Children ages 3 to 16 years • Controlled studies, pre-post studies, and single subject design	• Externalizing behavior	79 studies	• CBT was beneficial in all studies designs • Parent reported outcomes may inflate effectiveness
Lundahl, B. W., et al. (2006)[15]	Parent training programs	• For studies of children with ADHD, had to include a outcome for DBD separate from ADHD • Controlled studies reporting means and SDs, pre and post treatment for intervention and control groups	• Child disruptive behavior • Parent behavior • Parental perception	63 studies (69 behavioral experimental groups and 14 nonbehavioral experimental groups)	• Parent training was least effective for economically disadvantaged families • Individually delivered parent training compared to group delivery was more effective for low SES families
Thomas, R. and M. J. Zimmer-Gembeck (2007)[16]	Parent-Child Interaction Therapy and Triple P-Positive Parenting Program	• Children ages 3 to 12 years	•	24 studies	• Positive effects of both interventions, but effects varied depending on intervention length, components, and source of outcome data.
Sanders, M. R., et al. (2014)[17]	Triple P-Positive Parenting Program	• 1979-2013 • RCTs, non-RCTs, and uncontrolled studies	• Child behavior • Parenting practice • Parenting satisfaction	116 studies 101 studies (16,099 families) analyzed quantitatively	• Study approach, study power, Triple P level, and baseline severity of child problems produced moderated the intervention effects
Reyno, S. M. and	Parenting training	• 1980-2004	• Child disruptive	31 studies	• Maternal mental health and SES

Author, Year	Focus Area	Inclusion Criteria	Outcome(s)	# Studies Included	Key Findings
P. J. McGrath (2006)[18]		• Prevention and treatment studies	behavior • Child, parent and family variables that predict treatment outcome and dropout		were predictors of treatment response
Nowak, C. and N. Heinrichs (2008)[19]	Triple P Positive Parenting Program	• 1970-2007 •	• Parenting skill, child problem behavior or parent-child wellbeing using a validated scale •	55 studies (11, 797 families)	• larger effects found on parent report as compared to observational measures • Greater intervention effects associated with intensive formats and initially more distressed families.
Leijten, P., et al. (2013)[20]	Parent training	• Before 1/31/2010 • Children aged 12 and younger	• Child disruptive behavior reported as mean and SD on a standardized measure • SES and baseline DBD severity as predictors of intervention effectiveness	75 studies	• SES interaction with baseline severity • Samples of disadvantaged families with lower baseline severity benefitted less from parent management training than non-disadvantaged families with lower baseline severity DBD. SES did not predict effect sizes for patients with severe DBD at baseline
Kaminski, J. W., et al. (2008)[21]	Parent training	• 1990-2002 • Unclear if nonrandomized studies were included • Children aged 7 and younger	• Parenting measures • Child measures • Parent-child interaction	77 studies including 45 RCTs	• Increasing positive parent-child interactions and emotional communication skills, teaching parents to use time out and parenting consistency, and parental practice of new skills with their children during parent training sessions were associated with larger effects.
Forehand, R., et al. (2014)[22]	Behavioral Parent Training	• Children ages 2 to 18 years • Intervention and prevention • RCTs	• Parenting behavior • Child externalizing behavior	16 studies (3 intervention and 13 prevention studies)	•

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Appendix G. Applicability Tables

Table G-1. Applicability of evidence for psychosocial interventions

Domain	Description of applicability of evidence
Population	The population studied included children from ages 1.5 - 18 years, inclusive, and 72% male. The inclusion criteria varied from strict diagnostic criteria for a disruptive behavior disorder (typically ODD) to more vague assessments of disruptive behaviors typically operationalized as above a clinical cutoff on a well-validated parent-report measure.
Intervention	Psychosocial interventions for disruptive behaviors included interventions with a child, parent, or family component (single component interventions) and multicomponent interventions that included more than one of those individual components. Within each of these broad categories, individual interventions were heterogeneous.
Comparators	The studies compared active treatment to treatment as usual or to a wait list control group.
Outcomes	Parent report of child disruptive behaviors was by far the most commonly reported outcomes. The CBCL externalizing subscale, ECBI Intensity subscale, ECBI Problem subscale, and SDQ were the most commonly used parent-reported measures. Child self-report, teacher report, and direct observations of child disruptive behaviors were reported. Measures of functional outcomes were far less common.
Setting	The vast majority of studies was in the outpatient setting and generally carried out at academic medical centers in the United States. Several studies were conducted at specialty centers including a psychiatric day treatment program and domestic violence shelter.

Table G-2. Applicability of evidence for antipsychotic medications

Domain	Description of applicability of evidence
Population	The population studied included children ages 6-17, inclusive, and 83% male. The inclusion criteria varied from strict diagnostic criteria of ODD and CD to more vague assessments of aggressive behavior "severe enough to warrant pharmacotherapy." One study [1] studied aggression in patients with ADHD exclusively.
Intervention	The intervention medications, Aripiprazole, Quetiapine, Risperidone, and Ziprasidone are not FDA approved for treatment of disruptive behavior in children, but are used routinely in clinical practice in the US.
Comparators	Only one of the studies (5102) studied two medications head-to-head. The other studies compared the active medication to placebo.
Outcomes	The most common measures were the OAS and CGI. The OAS specifically addresses aggressive behavior symptoms and the CGI addresses improvement of symptoms compared to baseline.
Setting	The studies were all in the outpatient setting and generally carried out at academic medical centers in the US, with one (5102) at a community outpatient clinic.

Notes: Abbreviations: ADHD – Attention Deficit Hyperactivity Disorder; CD – Conduct Disorder; CGI – Clinical Global Impression; OAS – Ongoing Abuse Screen; ODD – Oppositional Defiant Disorder

Table G-3. Applicability of evidence for antiepileptic medications

Domain	Description of applicability of evidence
Population	The population studied included children from ages 6 to 18 years, inclusive, and 90% male.
Intervention	The intervention, valproic acid, is not FDA approved for disruptive behaviors in children, but is used in clinical practice in the US.
Comparators	Valproic acid compared to placebo or to low dose valproic acid.

Outcomes	The most common measures were the OAS and CGI. The OAS specifically addresses aggressive behavior symptoms and the CGI addresses improvement of symptoms compared to baseline.
Setting	The largest of the three studies (n=58) analyzed patients from a correctional facility, which indicates a higher acuity of disruptive behaviors. The other studies were conducted in outpatient clinics.

Table G-4. Applicability of evidence for nonstimulant medications

Domain	Description of applicability of evidence
Population	The population studied included school-aged children and adolescents, ages 6-17 years, and mostly male (69%-92%). Inclusion criteria included specifically children with ADHD and co-morbid ODD based on strict diagnostic criteria of ODD/CD.
Intervention	The intervention medications include the selective norepinephrine reuptake inhibitor atomoxetine and Guanfacine extended release, a selective central alpha2A-adrenergic receptor agonist; both of which are approved for the treatment of ADHD, but are not FDA approved for treatment of disruptive behavior in children.
Comparators	All studies compared the active medication to placebo. One study (665) had three arms that compared fast to slow titration of atomoxetine with target dose in both arms of 1.2mg/kg/d.
Outcomes	Primary outcomes were the change from baseline in the Swanson, Nolan, and Pelham Rating Scale-Revised (SNAP-IV) ODD subscore, or the oppositional subscale of the Conners Parent Rating Scale-Revised: Long Form (CPRS-R: L) measured at 8-9 weeks of treatment.
Setting	The studies were all in the outpatient setting at centers in the US, Germany, and Italy.

Table G-5. Applicability of evidence for ADHD stimulant medications

Domain	Description of applicability of evidence
Population	The population studied included school-aged children and adolescents, 6-17 years; and mostly male (69-90%). Patient population had ODD symptoms based on strict diagnostic criteria; and majority had co-morbid ADHD (66% to 79%)
Intervention	The intervention medications included methylphenidate and mixed amphetamine salts extended release (MAS XR); both of which are approved for treatment of ADHD; but are not FDA approved for disruptive behaviors in children.
Comparators	All studies compared the active medication to placebo. One study (1650) compared four different doses of MAS XR (10 mg, 20 mg, 30 mg, and 40 mg/d) to placebo.
Outcomes	Primary outcomes were the ODD subscore of the SNAP-IV and parent and teacher ratings of CD symptoms based on the Conners Teacher Rating Scale, and subscales of the Quay revised behavior problem checklist, measured after 4-5 weeks of treatment.
Setting	The two studies were conducted in the outpatient setting at centers in the US.

Appendix H. Reasons for Exclusion

Exclusion Code	Exclusion Reason	Count
X-1	Not original research	67
X-2	Does not measure the relationship between a psychosocial or pharmacologic intervention and an outcome	158
X-2a	Not an eligible study design	9
X-3	Not youth	30
X-4	No standardized disruptive behavior disorder classification or symptom assessment meeting a clinical threshold cutoff	319
X-4a	At-risk population or preventive intervention	5
X-5	Not conducted in an outpatient healthcare setting	177
X-6	Does not include an alternate treatment or control group for comparison to measure effectiveness	256
X-7	Does not report an outcome of interest for the population (youth) with disruptive behavior	125
X-7a	Does not report data for an outcome of interest by group	7
X-8	Does not address a Key Question	134
X-9	Duplicate	7
X-10	Unavailable	28
X-11	Older than 20 years	198
X-12	Non-English	5

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Appendix I. Pharmacologic Approval Status, Harms, and Indications

The harms data provided in this section were gathered from analyzing available gray literature (i.e. package inserts and FDA review packages). FDA approval packages were limited to those available on the FDA website that contained a "Medical Review" section of the document. Upon further analysis, approval packages that did not assess pediatric safety data were not included. Table I-1 includes the pediatric indication for medications referenced in the clinical studies included in this review. Medications that have not been approved as safe and effective in pediatric patients; therefore are only FDA approved in adults are referenced in Table I-2. Notable boxed warnings, contraindications, and warnings/precautions that would be relevant to consider in the pediatric population were included. As a result, the data provided in this chart is not an all-inclusive list of these package insert sections. For complete data please see the corresponding package insert.

Updated: September 28, 2014

Table I-1. FDA-approved pediatric medications included in literature review

Drug	FDA Approved Pediatric Indication	Boxed Warning	Contraindications	Warnings/ Precautions
Guanfacine [1]	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications	---	---	● Dose-dependent decreases in blood pressure and heart rate. ● Somnolence and sedation
Divalproex sodium [2]	● Treatment of manic episodes associated with bipolar disorder ● Monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures; adjunctive therapy in patients with multiple seizure types that include absence seizures ● Prophylaxis of migraine headaches	● Hepatotoxicity, including fatalities, usually during the first 6 months of treatment. Children under the age of two years and patients with mitochondrial disorders are at higher risk. ● Pancreatitis, including fatal hemorrhagic cases.	● Hepatic disease or significant hepatic dysfunction, ● Known mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG), ● Suspected POLG-related disorder in children under two years of age, ● Urea cycle disorders.	● Suicidal behavior or ideation ● Thrombocytopenia; monitor platelet counts and coagulation test. ● Hyperammonemia and hyperammonemic encephalopathy; measure ammonia level if unexplained lethargy and vomiting or changes in mental status, and also with concomitant topiramate use; consider discontinuation of therapy. ● Hypothermia
Aripiprazole [3]	● Treatment of schizophrenia: Adolescents (ages 13-17) ● Acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate: Pediatric Patients (ages 10-17) ● Treatment of irritability associated with autistic disorder: Pediatric Patients (ages 6-17 years)	● Children, adolescents, and young adults are at increased risk of suicidal thinking and behavior when taking this medication.	---	● Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring. ● Tardive Dyskinesia: Discontinue if clinically appropriate. ● Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain ● Orthostatic Hypotension: Use with caution in patients with known cardiovascular or cerebrovascular disease ● Leukopenia, Neutropenia, and Agranulocytosis: Patients with a history of a clinically significant low

Drug	FDA Approved Pediatric Indication	Boxed Warning	Contraindications	Warnings/ Precautions
				white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of aripiprazole should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. ● Seizures/Convulsions: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. ● Potential for Cognitive and Motor Impairment: Use caution when operating machinery. ● Suicide: The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder.
Atomoxetine [4]	Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD)	Increased risk of suicidal ideation in children or adolescents	● Atomoxetine use within 2 weeks after discontinuing MAOI or other drugs that affect brain monoamine concentrations. ● Pheochromocytoma or history thereof ● Severe Cardiovascular Disorders that might deteriorate with clinically important increases in HR and BP.	● Severe Liver Injury – Should be discontinued and not restarted in patients with jaundice or laboratory evidence of liver injury. ● Serious Cardiovascular Events – Sudden death, stroke and myocardial infarction have been reported in association with atomoxetine treatment. Patients should have a careful history and physical exam to assess for presence of cardiovascular disease. Atomoxetine generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to its

Drug	FDA Approved Pediatric Indication	Boxed Warning	Contraindications	Warnings/ Precautions
				noradrenergic effects. ● Emergent Cardiovascular Symptoms – Patients should undergo prompt cardiac evaluation. ● Effects on Blood Pressure and Heart Rate – Increase in blood pressure and heart rate; orthostasis and syncope may occur. Use with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease. ● Emergent Psychotic or Manic Symptoms – Consider discontinuing treatment if such new symptoms occur. ● Bipolar Disorder – Screen patients to avoid possible induction of a mixed/manic episode. ● Aggressive behavior or hostility should be monitored. ● Effects on Urine Outflow – Urinary hesitancy and retention may occur. ● Priapism – Prompt medical attention is required in the event of suspected priapism. ● Growth – Height and weight should be monitored in pediatric patients. ● Concomitant Use of Potent CYP2D6 Inhibitors or Use in patients known to be CYP2D6 PMs – Dose adjustment of atomoxetine may be necessary.
Amphetamine-Dextroamphetamine [5]	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) and Narcolepsy	● Administration of amphetamine for prolonged periods of time may lead to drug dependence due to the high risk of abuse and must be avoided ● Misuse of amphetamine	● Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or	● Serious Cardiovascular Events: Sudden Death and Pre Existing Structural Cardiac Abnormalities or Other Serious Heart Problems ○ Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with

Drug	FDA Approved Pediatric Indication	Boxed Warning	Contraindications	Warnings/ Precautions
		may cause sudden death and serious cardiovascular adverse events.	idiosyncrasy to the sympathomimetic amines, glaucoma. ● Agitated states. ● Patients with a history of drug abuse. ● During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).	structural cardiac abnormalities or other serious heart problems. ○ Hypertension and Other Cardiovascular Conditions: Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. ○ Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications: Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). ● Psychiatric Adverse Events ○ Preexisting Psychosis: Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder. ○ Bipolar Disorder: Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/

Drug	FDA Approved Pediatric Indication	Boxed Warning	Contraindications	Warnings/ Precautions
				manic episode in such patients. ○ Emergence of New Psychotic or Manic Symptoms: Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. ○ Aggression: Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the post-marketing experience of some medications indicated for the treatment of ADHD. ○ Long-Term Suppression of Growth: Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this

Drug	FDA Approved Pediatric Indication	Boxed Warning	Contraindications	Warnings/ Precautions
				period of development. ○ Seizures: there is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. ○ Visual disturbances: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. ● Should be used with caution in patients who use other sympathomimetic drugs. ● Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. ● Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.
Methylphenidate [6]	Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.	---	● Marked anxiety, tension, and agitation since the drug may aggravate these symptoms. ● Glaucoma ● Motor tics or with a family history or diagnosis of Tourette's syndrome. ● Treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days	● Serious Cardiovascular Events: ○ Sudden Death and Preexisting Structural Cardiac Abnormalities or Other Serious Heart Problems - Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. ○ Hypertension and Other

Drug	FDA Approved Pediatric Indication	Boxed Warning	Contraindications	Warnings/ Precautions
			following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).	Cardiovascular Conditions Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. ○ Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). ● Psychiatric Adverse Events ○ Pre-existing Psychosis: Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder. ○ Bipolar Disorder: Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/ manic episode in such patients. ○ Emergence of New Psychotic or Manic Symptoms: Treatment

Drug	FDA Approved Pediatric Indication	Boxed Warning	Contraindications	Warnings/ Precautions
				emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. ○ Aggression: Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the post-marketing experience of some medications indicated for the treatment of ADHD. ● Long-term suppression of growth: Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. ● Seizures: There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very

Drug	FDA Approved Pediatric Indication	Boxed Warning	Contraindications	Warnings/ Precautions
				rarely, in patients without a history of seizures and no prior EEG evidence of seizures. ● Priapism: Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. ● Peripheral Vasculopathy, Including Raynaud's Phenomenon: Stimulants, including methylphenidate, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. ● Visual Disturbance: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. ● Use in Children Under Six Years of Age: should not be used in children under 6 years, since safety and efficacy in this age group have not been established. ● Drug Dependence methylphenidate should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Drug	FDA Approved Pediatric Indication	Boxed Warning	Contraindications	Warnings/ Precautions
				● Patients with an element of agitation may react adversely; discontinue therapy if necessary. ● Periodic CBC, differential, and platelet counts are advised during prolonged therapy. ● Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of 1 or more of the behavioral characteristics. When these symptoms are associated with acute stress reactions, treatment with methylphenidate is usually not indicated.
Quetiapine [7]	● Schizophrenia ● Bipolar I disorder manic episodes ● Bipolar disorder, depressive episodes	Suicidal Thoughts and Behaviors: Increased risk of suicidal thoughts and behavior in children, adolescents, and young adults taking antidepressants.	---	● Neuroleptic Malignant Syndrome (NMS): Manage with immediate discontinuation and close monitoring ● Metabolic Changes: Atypical antipsychotics have been associated with metabolic changes. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. ● Tardive Dyskinesia: Discontinue if clinically appropriate. ● Hypotension: Use with caution in patients with known cardiovascular or cerebrovascular disease. ● Increased Blood Pressure in Children and Adolescents: Monitor blood pressure at the beginning of, and

Drug	FDA Approved Pediatric Indication	Boxed Warning	Contraindications	Warnings/ Precautions
				periodically during treatment in children and adolescents ● Leukopenia, Neutropenia and Agranulocytosis: Monitor complete blood count frequently during the first few months of treatment in patients with a preexisting low white cell count or a history of leukopenia/neutropenia and discontinue at the first sign of a decline in WBC in absence of other causative factors. ● Cataracts: Lens changes have been observed in patients during long-term quetiapine treatment. Lens examination is recommended when starting treatment and at 6-month intervals during chronic treatment. ● Hypothyroidism: In controlled trials in children and adolescent patients with schizophrenia or bipolar mania, the incidence of shifts for thyroid function values at any time for quetiapine treated patients and placebo-treated patients for elevated TSH was 2.9% (8/280) vs. 0.7% (1/138), respectively and for decreased total thyroxine was 2.8% (8/289) vs. 0% (0/145, respectively). ● Hyperprolactinemia: In controlled trials in children and adolescent patients with bipolar mania or schizophrenia, the incidence of shifts in prolactin levels to a value (>20 µg/L males; > 26 µg/L females at any time) was 13.4% (18/134) for quetiapine compared to 4% (3/75) for placebo in males and 8.7% (9/104) for quetiapine compared to 0% (0/39) for placebo in females. ● Potential for Cognitive and Motor

Drug	FDA Approved Pediatric Indication	Boxed Warning	Contraindications	Warnings/ Precautions
				Impairment - Since quetiapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness.
Risperidone [8]	• Treatment of schizophrenia. Efficacy was established in 2 short-term trials in adolescents (ages 13 to 17 years) • Treatment (montherapy) of acute manic or mixed episodes associated with Bipolar I Disorder. Efficacy was established in one short-term trial in children and adolescents (ages 10 to 17 years) • Treatment of irritability associated with autistic disorder, including symptoms of aggression towards others, deliberate selG-injuriousness, temper tantrums, and quickly changing moods. Efficacy was established in 3 short-term trials in children and adolescents (ages 5 to 17 years)	---	---	• Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring. • Tardive dyskinesia: Consider discontinuing if clinically indicated. • Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/ cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. • Hyperprolactinemia: Prolactin elevations occur and persist during chronic administration. • Orthostatic hypotension: For patients at risk, consider a lower starting dose and slower titration. • Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts in patients with a history of clinically significant low white blood cell count (WBC). Consider discontinuing if a clinically significant decline in WBC occurs in the absence of other causative factors. • Potential for cognitive and motor impairment: Use caution when operating machinery. • Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

Table I-2. FDA-approved adult medications (prescribed off label in pediatric patients) included in literature review

Drug	FDA Approved Adult Indication	Boxed Warning	Contraindications	Warnings/ Precautions
Ziprasidone [9]	• Treatment of schizophrenia. • Acute treatment as monotherapy of manic or mixed episodes associated with bipolar I disorder • Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate. • Acute treatment of agitation in schizophrenic patients.	---	• Do not use in patients with a known history of QT prolongation. • Do not use in patients with recent acute myocardial infarction • Do not use in patients with uncompensated heart failure • Do not use in combination with other drugs that have demonstrated QT prolongation.	• QT Interval Prolongation: should be avoided in patients with bradycardia, hypokalemia or hypomagnesemia, congenital prolongation of the QT interval, or in combination with other drugs that have demonstrated QT prolongation • Neuroleptic Malignant Syndrome (NMS): Potentially fatal symptom complex has been reported with antipsychotic drugs. Manage with immediate discontinuation of drug and close monitoring. • Tardive Dyskinesia - May develop acutely or chronically • Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. • Rash: Discontinue in patients who develop a rash without an identified cause • Orthostatic Hypotension: Use with caution in patients with known cardiovascular or cerebrovascular disease • Leukopenia, Neutropenia, and Agranulocytosis has been reported with antipsychotics. Patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should

Drug	FDA Approved Adult Indication	Boxed Warning	Contraindications	Warnings/ Precautions
				discontinue at the first sign of a decline in WBC in the absence of other causative factors. ● Seizures: Use cautiously in patients with a history of seizures or with conditions that lower seizure threshold ● Potential for Cognitive and Motor impairment: Patients should use caution when operating machinery ● Suicide Closely supervise high-risk patients

Table I-3. Serious adverse events reported across medications*

	Guanfacine	Divalproex	Aripiprazole	Atomoxetine	Amphetamine / Dextroamphetamine	Methylphenidate	Quetiapine	Risperidone	Ziprasidone
Suicide attempt			●					●	●
Suicidal ideation			●	●					
QT prolongation	●			●			●	●	●
Death	●			●	●	●		●	
Stroke				●	●				
Myocardial Infarction	●			●	●				●
Orthostatic hypotension	●		●					●	●
Angioedema			●	●	●			●	●
Cardiac arrest	●								
Neuroleptic malignant syndrome			●			●	●	●	●
Steven-Johnson syndrome					●		●		
Mania/hypomania	●				●	●		●	●
Extrapyramidal symptoms/ disorder			●				●	●	●
Tardive dyskinesia		●	●				●	●	●
Abnormal LFTs				●					
Respiratory system disorders								●	●
Pancreatitis		●					●	●	
Seizures/ convulsions	●		●	●	●	●		●	●
Syncope	●			●			●		●

*Events gathered from all available harms data including: clinical trial data and post-marketing experience

Table I-4. Selected adverse events observed across medications*

	Guanfacine	Divalproex Sodium	Aripiprazole	Atomoxetine	Amphetamine-Dextroamphetamine	Methylphenidate	Quetiapine	Risperidone	Ziprasidone
Somnolence	●	●	●	●			●	●	●
Weight Loss		●		●	●	●			
Weight Gain	●	●	●				●	●	●
Tachycardia	●	●		●	●	●	●		●
Decrease alkaline phosphatase				●					
Hyperprolactinemia							●	●	
Aggression	●		●	●	●	●	●		
Hypotension	●	●					●	●	
Hypertension	●	●		●	●	●			
Decreased heart rate	●								
Increased heart rate				●	●	●	●	●	
Dyslipidemia			●				●	●	●
Hyperglycemia			●				●	●	●
Leukopenia			●	●		●	●	●	●
Neutropenia			●				●	●	●

*Events gathered from all available harms data including: clinical trial data and post-marketing experience

Table I-5. Pharmacologic agents considered for DBD review

Drug Class Individual agent (proprietary name)		
Alpha-agonists	**First-generation antipsychotics**	**Selective serotonin reuptake inhibitors (SSRI)**
• Clonidine	• Chlorpromazine	• Fluoxetine
• Guanfacine (Intuniv®)	• Fluphenazine	• Sertraline
	• Haloperidol	• Citalopram
Anticonvulsants	• Loxapine	• Escitalopram
• Carbamazepine (Tegretol®)	• Perphenazine	• Paroxetine
• Oxcarbazepine (Trileptal®)	• Prochlorperazine	• Fluvoxamine
• Divalproex sodium (Depakote®)	• Thiothixene	
• Lamotrigine (Lamictal®)	• Thioridazine	
• Valproate/ Valproic acid	• Trifluoperazine	
Beta-blockers	**Second-generation (atypical) antipsychotics**	**Other (e.g., antihistamines, benzodiazepines, mood stabilizers, non-SSRI antidepressants)**
• Propranolol	• Aripiprazole (Abilify®)	• Lithium
• Metoprolol	• Asenapine (Saphris®)	• Atomoxetine (Strattera®)
• Pindolol	• Clozapine (Clozaril®)	• Naltrexone
• Nadolol	• Iloperidone (Fanapt®)	• Hydroxyzine
	• Lurasidone (Latuda®)	• Clonazepam (Klonopin®)
Central nervous system (CNS) stimulants	• Olanzapine (Zyprexa®)	• Levetiracetam (Keppra®)
• Amphetamine-Dextroamphetamine (Adderall®)	• Olanzapine/Fluoxetine (Symbyax®)	• Lorazepam (Ativan®)
• Methylphenidate (Ritalin®)	• Paliperidone (Invega®)	• Bupropion
• Lisdexamfetamine (Vyvanse®)	• Quetiapine (Seroquel®)	
	• Risperidone (Risperdal®)	
	• Ziprasidone (Geodon®)	

Table I-6. FDA approval status for drugs included in the DBD review

Generic Name (Trade Name)	Indication(s)	Approved For
Amphetamine Salts (Adderall)	Attention Deficit Hyperactivity Disorder (ADHD)	Children (3 +)
	Narcolepsy	Children (6 +)
Aripiprazole (Abilify)[10]	Schizophrenia	Adults and adolescents (13–17 years)
	Bipolar disorder (manic/mixed) monotherapy or adjunctive to lithium or valproate	Adults and children (10–17 years)
	Adjunctive treatment of major depressive disorder	Adults
	Irritability Associated with autistic disorder	Children (6–17 years)
	Acute treatment of agitation	Adults
Atomoxetine (Strattera)[11]	Attention Deficit Hyperactivity Disorder (ADHD)	Adults and children (6-18)
Divalproex (Depakote)	Bipolar Disorder (manic episodes)	Adults and children (10 +)
	Seizures	
	Migraine Headaches	
Guanfacine (Intuniv)[12]	Attention Deficit Hyperactivity Disorder (ADHD) and adjunctive therapy to stimulant medications	Children and adolescents (6-17)
Methylphenidate (Ritalin)	Attention Deficit Disorders (ADD)	Children and adults (6 + years)
Quetiapine (Seroquel)[13]	Schizophrenia	Adults and adolescents (13–17 years)
	Bipolar disorder (acute manic)	Adults, children, and adolescents (10–17 years)
	Bipolar disorder (depression)	Adults
	Bipolar disorder (maintenance)	
	Adjunctive therapy for major depressive disorder	
Risperidone (Risperdal)[14]	Schizophrenia	Adults and adolescents (13–17 years)
	Bipolar disorder (manic/mixed)	Adults and adolescents (10–17 years)
	Irritability associated with autism	Children (5–16 years)
Valproate/Valproic Acid (Depacon)	Epilepsy	Children and adults (10 + years
Ziprasidone (Geodon)	Schizophrenia	Adults
	Bipolar disorder (manic/mixed)	
	Bipolar disorder (maintenance)	
	Acute agitation in patients with schizophrenia	

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Appendix J. Key Question 1 Evidence Profile

Table J-1. Evidence summary of psychosocial intervention effects on parent-rated disruptive behavior in studies of preschool age children

Studies	N	Risk of Bias	Intervention vs. Control	Head-to-Head Comparison	SOE *Comments*
Child Only (n=0)					
NA	NA	NA	NA	NA	O
Parent Only (n=14)					
RCT: 13[1-13]	(1466)	Low: 1[8] Moderate: 7[1,3,6,7,9,10,13] High: 5[2,4,5,11,12]	Outcomes consistently improved in intervention arms compared with waitlist or treatment as usual controls. **Significant:** Intervention > WLC or TAU (9)[1,3 ,6-12] **Nonsignificant:** Intervention > TAU (1)[13]	Differences between modified versions of the same intervention were typically not significant. **Significant:** Intervention vs. modified intervention (1)[7] **Nonsignificant:** Intervention vs. modified intervention (4)[2,4,5,10]	++
NRCT: 1[14]	(144)	Moderate: 1[14]	**Nonsignificant:** Intervention > WLC or TAU (1)[14]	NA	O
Multicomponent (n=9)					
RCT: 9	(401)	Low: 1[15] Moderate: 3[16-18] High: 5[19-23]	Outcomes consistently improved in intervention arms compared with waitlist or treatment as usual controls. **Significant:** Intervention > WLC or TAU (**8**)[15-22]	Differences between modified versions of the same intervention were typically not significant. **Nonsignificant:** Intervention vs. modified intervention (3)[15,16,23]	++

O = Insufficient, + = Low, ++ = Moderate, +++ = High

Table J-2. Evidence summary of psychosocial intervention effects on parent-rated disruptive behavior in studies of school age children

Studies	N	Risk of Bias	Intervention vs. Control	Head-to-Head Comparison	SOE *Comments*
Child Only (n=1)					
RCT: 1[1]	(97)	Low: 0 Moderate: 1[1] High: 0	Outcomes improved in intervention arms compared with waitlist control group **Significant:** SCIP, SST > WLC (1)[1]	Differences between the active intervention groups were not significant **Nonsignificant:** SCIP > SST (1)[1]	O
Parent Only (n=11)					
RCT: 8[2-9]	(995)	Low: 1[4] Moderate: 5[5-9] High: 2[2,3]	Outcomes significantly improved in intervention groups vs. control **Significant:** (6)[2-7]	Differences between modified versions of the same intervention were not significant **Nonsignificant:** (3)[5,8,9]	++
Cohort: 3[10-12]	(334)	Low: 0 Moderate: 0 High: 3[10-12]	Outcomes significantly improved in intervention groups vs. control **Significant:** Intervention > TAU (1)[10] **Nonsignificant:** Intervention vs. TAU (1)[11]	Differences between modified versions of the same intervention were significant **Significant:** PMT skilled > PMT perceptive (1)[12]	+
Multicomponent (n=17)					
RCT: 15[13-27]	(1685)	Low: 1[15] Moderate: 11[13,14,17-22,24-26] High: 3[16,23,27]	Improved from baseline in most active treatment arms but between group changes not consistently significantly different **Significant:** (4)[16,20,24,27] **Nonsignificant:** (5)[13,14,19,23,26] **Inconsistent:** (2)[15,18]	Improved from baseline in most active treatment arms but between group changes not consistently significantly different **Significant:** (2)[20,25] **Nonsignificant:** (3)[17,21,26] **Inconsistent:** (1)[22]	+ *Inconsistent outcomes reported by different measures/ rating scales*
Cohort: 2[28,29]	(474)	Low: 0 Moderate: 1[29] High: 1[28]	Outcomes significantly improved in intervention groups vs. WLC or TAU **Significant:** (2)[28,29]	NA	++

O = Insufficient, + = Low, ++ = Moderate, +++ = High

Table J-3. Evidence summary of psychosocial intervention effects on parent-rated disruptive behavior in studies of teenage children

Studies	N	Risk of Bias	Intervention vs. Control	Head-to-Head Comparison	SOE *Comments*
Child Only[a] (n=1)					
RCT: 1[1]	(93)	Low: 0 Moderate: 0 High: 1[1]	Intervention > Control **Significant:** (1)[1]	NA	O
Parent Only (n=0)					
NA	NA	NA	NA	NA	O
Multicomponent (n=13)					
RCT: 12[2-13]	(1294)	Low: 4[3,4,8,9] Moderate: 5[2,7,10,11,13] High: 3[5,6,12]	Most studies reported improved outcomes in treatment arms versus control arms. **Significant:** (10)[2-4,6-11,13]	Differences between interventions were significant. **Significant:** (2)[5,12]	++
Cohort: 1[14]	(192)	Low: 0 Moderate: 0 High: 1[14]	NA	**Nonsignificant:** CBT vs. FFT vs. CBT + Parent training (1)[14]	O *Outcome: recidivism*

O = Insufficient, + = Low, ++ = Moderate, +++ = High

Table J-4. Evidence profile for studies included in the meta-analysis

Intervention Category (arms)	Total N	Effect measure	Probability of being best	Overall SOE
TAU/WLC (n=50)	1348	NA	NA	• Strong evidence that of the 4 arms, this is the inferior
Child only (n=6)	190	−1.0 (95% credible interval: −1.6 to −0.4)	15	• Strong evidence that each of these are better than TAU • Weak evidence that of these 3 arms multi-component and parent only are best
Parent only (n=41)	1540	−1.2 (95% credible interval: −1.6 to −0.9)	43	
Multicomponent (n=32)	929	−1.2 (95% credible interval: −1.6 to −0.9)	43	

Notes: Table represents quantitative mixed effects model of a subset of studies from qualitative review. The model included RCTs that reported baseline and end-of-treatment group mean and standard deviation from ECBI- Intensity, ECBI- Problem, and/or CBCL- Externalizing T-score). For more details on the selection of studies, see the methods in the Full Report.

Includes studies from KQ1 for children of all ages (i.e., psychosocial interventions for preschool age, school age, and teenage participants).The treatment arms of each study were classified as one of the following types: 1) interventions including only a child component; 2) interventions including only a parent component; and 3) multicomponent interventions. Those not identified by any of these three classes were considered either control or treatment-as-usual arms. The number of arms exceeds the number of included studies as studies could contribute data from more than one arm per intervention type.

The effect sizes estimated by the model can be interpreted as the expected change in score for the intervention category relative to treatment as usual or control.

This summary does not include risk of bias ratings, as those assessments are made at the individual study level, and not at the level of a treatment arm.

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