Editorial Perspective

Roest, Annelieke M.; de Vries, Ymkje Anna; Wienen, Albert W.; de Jonge, Peter

Published in:
Journal of child psychology and psychiatry and allied disciplines

DOI:
10.1111/jcpp.13677

The Journal of Child Psychology and Psychiatry

Journal of Child Psychology and Psychiatry **:* (2022), pp **–** doi:10.1111/jcpp.13677

Editorial Perspective: Are treatments for childhood mental disorders helpful in the long run? An overview of systematic reviews

Annelieke M. Roest,[1,2] Ymkje Anna de Vries,[1,2] Albert W. Wienen,[3] and Peter de Jonge[1,2]

[1]Department of Developmental Psychology, Faculty of Behavioral and Social Sciences, University of Groningen, Groningen, The Netherlands; [2]Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE), University Medical Center Groningen (UMCG), University of Groningen, Groningen, The Netherlands; [3]Windesheim University of Applied Sciences, Zwolle, The Netherlands

Introduction

Mental health problems are prevalent and often have severe consequences for individuals across the lifespan. Problems associated with childhood psychopathology are particularly long-lasting, including the development of comorbidity, disability, suicidality, and lower educational and vocational attainment (Costello & Maughan, 2015). Therefore, the importance of recognition and intervention for children with emotional or behavioral disorders has been stressed, especially since, at least in theory, treatment may prevent lifelong suffering from these disorders and the development of other mental health problems later in life (Kendall & Kessler, 2002), and thereby prevent a 'cascade of psychopathology' (Wehry, Beesdo-Baum, Hennelly, Connolly, & Strawn, 2015). However, although effective treatments exist for the treatment of emotional or behavioral disorders in young people, little is known about their effects in the long run. Most randomized controlled trials (RCTs) on the efficacy of treatments for common childhood mental disorders have only focused on outcomes after several weeks to several months of treatment. Several observational studies, however, have suggested that children and adolescents who received treatment are worse off later in life than those with similar symptom levels who remained untreated (e.g., Jörg et al., 2012). Studies specifically focusing on psychopharmacology have also reported possible long-term side effects (e.g., Carucci et al., 2021). These findings raise the question of whether the treatment of common childhood mental disorders is beneficial in the long term.

A major obstacle to solving this question is how to make sense of the heterogeneous literature. Systematic reviews provide a comprehensive summary of the available evidence on a topic but are usually specific to a particular disorder or form of treatment. To answer the broad question regarding the long-term effectiveness of treatment of common childhood mental disorders, a question of utmost importance for policymakers and health care providers, we conducted an overview of systematic reviews. Our aim was to assess whether the treatment of common childhood mental disorders is effective and safe in the long term (i.e., ≥ 2 years). We discuss the available evidence for the long-term effectiveness and safety of treatments for common childhood mental disorders. We then reflect on two key issues: (1) methodological difficulties in establishing long-term treatment effects and (2) the risk–benefit ratio of treatments for common childhood mental disorders.

Available evidence

We performed a systematic search for systematic reviews on the long-term (≥2 years) effectiveness and harms of treatment for attention deficit hyperactivity disorder (ADHD), behavior, anxiety, and depressive disorders for children between 6 and 12 years old (see Appendices 1 and 2). Eighteen reviews met inclusion criteria, but 13 (72.2%) of these did not identify any studies with a long-term follow-up. This left us with five reviews that were included in the current overview: three focusing on ADHD (Carucci et al., 2021; Charach et al., 2011; Kazda et al., 2021) and two on behavior disorders including conduct disorder (CD), oppositional defiant disorder (ODD), and intermittent explosive disorder (IED) (Epstein et al., 2015; Pillay et al., 2018). We did not identify any systematic reviews providing evidence for the long-term treatment of childhood anxiety or depressive disorders.

Long-term treatment of ADHD

Evidence-based treatments of ADHD involve pharmacological and psychosocial interventions. Of the three included reviews on the long-term treatment of ADHD, two focused on both effectiveness and safety of pharmacological (Charach et al., 2011; Kazda et al., 2021) and psychosocial interventions (Charach et al., 2011) and included studies with various designs, such as RCTs, extension trials, withdrawal trials, and cohort studies. Because Kazda et al. (2021) focused on the ratio of benefits versus harms, specifically for youth with milder symptoms, their inclusion

Conflict of interest statement: No conflicts declared.

of studies and extraction of results was somewhat different from those by Charach et al. (2011). The topic of the third review concerned the effect of long-term exposure to methylphenidate on growth in children and adolescents (Carucci et al., 2021).

Pharmacological treatments for ADHD include stimulant medications (e.g., methylphenidate and amphetamine) and nonstimulant medication (e.g., atomoxetine and guanfacine extended release). Most primary studies examined stimulant medications. Regarding the long-term benefits of medications, the evidence is inconclusive, because few long-term studies included adequate comparison groups or adequate control for confounding (Charach et al., 2011). The best available evidence comes from the Multimodal Treatment Study of ADHD, an RCT that compared medication (usually methylphenidate), behavior treatment (parent-, child-, and school-based), combination treatment, and usual community care. Follow-up studies showed that the initial superiority of medication and combined treatment was no longer present at 3- and 8-years follow-up. All treatment groups improved over time, although not enough to match non-ADHD community peers (Charach et al., 2011). Kazda et al. (2021) also concluded that the benefits of pharmacological treatments decreased over time and that long-term effects are small, if present at all. In addition, benefits are probably even smaller in mild compared to severe cases (Kazda et al., 2021).

Nonpharmacological treatments for ADHD include psychosocial treatment of either the child and/or the parents or in some cases academic interventions in school settings. The effectiveness of these types of interventions in the long term is under-researched and therefore the evidence is inconclusive (Charach et al., 2011). No primary studies included information regarding the adverse effects of nonpharmacological treatments.

Pharmacological treatment of ADHD has mild to moderate side effects in the short-term, such as appetite reduction and sleep disruption, and is associated with high discontinuation rates, that is, 20–44% (Kazda et al., 2021). Evidence for adverse effects in the long-term is limited, mainly because of a lack of studies with a long-term follow-up and a proper comparison group. Carucci et al. (2021) specifically focused on the effects of long-term stimulant use on growth parameters and detected small to moderate height and weight suppression in children treated with stimulants, with weight reductions most prominent in the short term and height reductions at longer-term follow-ups. In most cases, the observed growth suppression is not of clinical significance, although for some children it could be (Carucci et al., 2021). According to Kazda et al. (2021), stimulant medications are associated with both height and weight suppression, although the evidence is not entirely consistent. Finally, regarding guanfacine extended release, monitoring of cardiac status may be indicated (clinically significant ECG changes occurred in 1% of participants) (Charach et al., 2011). Given the lack of evidence for clear long-term benefits, the harms of pharmacological treatment may outweigh the benefits, especially in the long term and in milder cases (Kazda et al., 2021).

Long-term treatment of behavior disorders

Psychosocial treatments of behavior disorders include child-level interventions such as social skills training, parent-level interventions such as parent management training, and multicomponent interventions, which target both the child and its parents and/or teachers. Concerning pharmacological treatments, while second-generation antipsychotics are prescribed most often, a wide range of drug classes have been studied, including antipsychotics, anticonvulsants, stimulants, and nonstimulants (Epstein et al., 2015). No drugs have received FDA or EMA approval for the treatment of behavior disorders, with the exception of risperidone for persistent aggression in conduct disorder in Europe.

Epstein et al. (2015) conducted a systematic review and meta-analysis on the effects of pharmacological and psychosocial interventions for disruptive behavior (e.g., as part of CD or ODD) in children and adolescents. This systematic review included studies with different designs, such as RCTs, extension trials, and cohort studies. A systematic review by Pillay et al. (2018) focused on the harms of first- and second-generation antipsychotics in the treatment of psychiatric and behavioral conditions in children, adolescents, and young adults and also included a variety of study designs, for example, RCTs, extension trials, cohort studies, and individual patient data meta-analyses.

Epstein et al. (2015) included a few small studies of antipsychotics and stimulants, which reported positive effects on disruptive behaviors in the short term. However, no studies with a follow-up long enough were available to conclude anything about the long-term effectiveness of treatment. Among psychosocial treatments, parent-level and multicomponent programs showed positive long-term effects, yet the number of studies was low and outcomes were not consistently positive (Epstein et al., 2015). In addition, studies uniformly failed to note whether the harms of psychosocial interventions were investigated (Epstein et al., 2015).

Antipsychotics prescribed for behavior disorders are associated with side effects such as extrapyramidal symptoms (particularly with first-generation antipsychotics), weight gain, sleepiness, sedation, and high triglyceride levels. Unfortunately, there are few studies with a long-term follow-up. However, second-generation antipsychotics have been found to also increase the risk for weight gain, high cholesterol, and type-2 diabetes in the long term (Pillay et al., 2018). Therefore, clinicians should

weigh the benefits and harms when prescribing antipsychotics, especially when alternatives exist (Pillay et al., 2018).

Long-term treatment of anxiety and depressive disorders

As mentioned before, we did not identify any systematic reviews that fit our inclusion criteria for anxiety or depressive disorders. Potential reasons for this lack of information, and implications as well as suggestions for future research are discussed in the paragraphs below.

Overview of (a lack of) systematic reviews

The impression that emerges from this overview is that there is no convincing evidence that interventions for the most common childhood disorders are beneficial in the long term. In addition, high withdrawal rates and exclusion of patients with a history of adverse events potentially distort findings of long-term studies on adverse effects of pharmacological treatments (Charach et al., 2011; Pillay et al., 2018), while reporting of potential negative effects of psychological treatments in primary studies is absent (Epstein et al., 2015). Virtually all reviews we discussed also concluded that there were few studies with a long-term follow-up available, often too few to allow firm conclusions. A potential reason for the lack of long-term studies is that many systematic reviews on treatment effects exclusively focused on RCTs, and RCTs with long-term follow-up periods are very scarce.

In conclusion, the scientific literature cannot answer the important policy and health care question regarding the long-term effectiveness and safety of treatment of childhood mental disorders with any confidence. We discuss potential methodological reasons in the next part of this editorial.

Methodological issues related to establishing long-term treatment effects

Establishing long-term benefits and harms of the treatment of childhood mental disorders is challenging because of several methodological complexities. Conducting RCTs with long-term follow-up is often not feasible, or unethical, since treatment cannot be systematically denied to participants in the control group (Kendall & Kessler, 2002). As a result, randomization is lost in long-term follow-up periods. Observational studies and open-label extensions of RCTs suffer from selection effects and confounding, for example, those that receive mental health treatment may be the most severe cases. Although some studies have tried to address such problems by means of sophisticated matching techniques (e.g., Jörg et al., 2012), confounding by indication remains a lurking problem in such studies. Other difficulties hampering this kind of research are developmental variability, the variability in the natural course of mental disorders, and in general the influence of various factors over time (Kendall & Kessler, 2002).

These methodological difficulties may make carrying out long-term effectiveness studies less attractive, as well as hard to publish in case findings are nonsignificant or negative. However, long-term studies are needed because short-term effects found in RCTs may not last beyond the duration of the trial or beyond its controlled setting and some adverse effects of treatment may become visible only after several years. On the other hand, the effectiveness of some interventions may also increase over the years, that is, 'sleeper effects'. Either way, it is important for healthcare practitioners, policymakers, and parents and children to have reliable information about the long-term effectiveness and safety of interventions for childhood mental disorders, also because scarce resources could otherwise be spent on alternatives to improve child mental health.

Future research could target some gaps in the available evidence identified in the present overview. The most obvious gap is the paucity of studies with a long-term follow-up, especially those that have a suitable comparison group. Additional suggestions for the design and reporting of long-term follow-up studies of RCTs include assessments of youth at multiple time points to examine within-person trajectories, inclusion of all randomized participants, and inclusion of functional outcomes besides diagnostic status and symptom severity measures. Furthermore, interim service use should be assessed in detail (Gibby, Casline, & Ginsburg, 2017). Further, large administrative databases, for example, as a result of routine outcome measuring, have become increasingly helpful in addressing issues of confounding, and these can be useful for studying real-world outcomes as well as rare adverse effects. The linkage of different databases, especially when measurements are standardized or harmonized, could further increase research possibilities. In addition, retrospective observational studies, such as the World Mental Health surveys, are useful in providing estimates on (differential) treatment effects in large groups of individuals (e.g., de Vries et al., 2021). Since retrospective studies may be affected by (recall) biases, results should, when possible, be validated in longitudinal designs. Observational studies may also include instrumental variable analysis, a method that is still relatively underused in psychiatry. Triangulation of evidence (Ohlsson & Kendler, 2020), that is, using multiple methods to answer the same question, for example, long-term follow-up studies of RCTs, retrospective and prospective observational studies, the use of instrumental variable analysis, and propensity scoring, may provide a better picture of the long-term effectiveness of treatments for childhood mental

disorders. Answers to these questions may guide policy decisions and influence public health.

Other problems present in short- and long-term effectiveness research could also be addressed in future research, such as nonrepresentativeness of study samples. In addition, more long-term studies could provide information on differences in effectiveness and safety between different drugs and psychological treatments (Coghill et al., 2021). Furthermore, the reporting of potential negative effects of psychological treatments in studies is highly uncommon (Epstein et al., 2015). However, such negative effects (e.g., worsening of symptoms, increased conflicts during parent management training) may be present (Coghill et al., 2021).

The risk–benefit ratio of treatment of common childhood mental disorders

We recommend that clinicians and parents, in conversation with affected children, weigh the potential short- and long-term benefits and harms of treatments. Decision-making is particularly difficult when little evidence exists for long-term treatment outcomes, as in the case of childhood depressive and anxiety disorders. While new-generation antidepressants are effective for the treatment of depressive and anxiety disorders in young people in the short term (Hetrick et al., 2021), on average they have only small effects. However, for some individuals, these effects may be of clinical significance (Hetrick et al., 2021). Nevertheless, treatment with cognitive behavioral therapy (CBT) should be considered. In case antidepressants are prescribed, their effects should be closely monitored when balancing benefits and harms (Hetrick et al., 2021), especially since these drugs are associated with increases in suicide-related thinking and behavior. In general, assessing and managing long-term side effects of pharmacotherapy are complex issues, although periodic drug monitoring and drug holidays have been recommended for ADHD (Carucci et al., 2021).

Besides drug effects, other adverse long-term effects of childhood treatments can result from stigma and self-fulling prophecy effects related to receiving a diagnostic label, as well as learned helplessness, or reductions in feelings of self-efficacy or self-esteem (Jörg et al., 2012). Also, in view of the evidence that the benefit-to-harm ratio of treatment may be especially unfavorable in cases with milder psychopathology, stepped care approaches may be a rational choice (Kazda et al., 2021). When treatment is deemed necessary, effective treatment may require multiple trials of different treatments and/or practitioners (de Vries et al., 2021), preferably in collaborative care or a multidisciplinary team (Coghill et al., 2021). In addition, booster sessions may contribute to more long-term beneficial effects to reach optimal outcomes (Costello & Maughan, 2015).

Other approaches

Our overview was restricted to studies on treatments for children with an established diagnosis. Therefore, it does not cover research done on primary prevention programs for children who do not have a mental disorder (yet). Especially in the context of depression, anxiety, and behavior problems, many studies examining the effects of primary prevention programs are available, either directed at high-risk children or at entire classrooms or schools. However, intervention effects are generally small, and long-term studies are also scarce in this area. Although such a preventative approach avoids the problems of stigma or self-fulfilling prophecies associated with diagnoses, it by necessity exposes a far greater population of children to intervention and its potential adverse effects. Relatedly, screening for anxiety and depressive disorders has been suggested, yet this may cause unintended harm and also uses up limited health care resources for young people with, on average, relatively mild symptoms.

A recent commission paper called for a whole-of-society-approach to the prevention of depressive disorder (Herrman et al., 2022). We believe this approach should be extended to other (childhood) mental disorders, especially since we know that externalizing and anxiety disorders often precede depression. Whole-of-society actions potentially causing a reduction in childhood mental disorders are key, for example, by addressing support for parenting, (unhealthy) lifestyles, bullying at school, gender inequalities, and reducing stigma (Herrman et al., 2022).

Conclusion

Although treatments for common childhood mental disorders have been shown to be effective in the short term, long-term benefits of psychosocial and pharmacological childhood interventions appear to be small at best, while long-term harms of pharmacological and psychosocial treatments cannot be ruled out. The paucity of long-term studies on the treatment of childhood mental disorders is a major gap in the scientific evidence and therefore an important direction for future research. In the absence of firm scientific evidence, the expected balance of benefits and harms in the short and long run for the individual child in his or her particular context should guide treatment decisions regarding ADHD, behavior, and anxiety or depressive disorders. In some cases, watchful waiting may be the best choice, especially if symptoms are mild.

Acknowledgements

Funding was provided by the municipality of Heerenveen. The funder had no influence on the design of the study or the decision to submit it for publication. This

article is based on research carried out by the authors' esteemed colleague Dr. Elisabeth (Elske) Bos who sadly passed away on September 13, 2021.

Correspondence

Annelieke M. Roest, Department Developmental Psychology, Faculty of Behavioural and Social Sciences, University of Groningen, Grote Kruisstraat 2/1, 9712 TS Groningen, The Netherlands;
Email: a.m.roest@rug.nl

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Appendix 1

Search strategy and inclusion and exclusion criteria

A systematic literature search (see Appendix 2 for the search string) in PubMed, PsycINFO, and SocINDEX was performed from 2011 up to April 26, 2021 and updated on March 9, 2022. We included systematic reviews on the long-term (≥2 years) effects and harms of pharmacological or psychosocial (targeting the child and/or the parents) treatment for common childhood mental disorders [ADHD, behavior disorders (ODD, CD, and IED), anxiety disorders, and depressive disorders]. Systematic reviews primarily focused on other psychiatric disorders or on psychiatric disorders comorbid to a primary somatic disorder were excluded, as were reviews focusing on samples of institutionalized, hospitalized, or delinquent children. Reviews focusing on the broader category of 'mental disorders' were included if the studies within the review included one or more of the disorder categories specified above. We limited our overview to research on children between 6 and 12 years old with an established diagnosis of a mental disorder (e.g., according to ICD or DSM criteria established during childhood or retrospectively). Reviews on effectiveness studies including a broader age range were included only if the above age range was covered as well and childhood results were discussed separately. Designs of the studies covered by the systematic reviews could consist of RCTs, follow-ups of RCTs (extension or withdrawal trials), or observational studies (retrospective and prospective cohort studies, case–control studies, case registries) that provided comparisons between a treatment and a control group consisting of children with the respective mental disorder. In the case of overlapping systematic reviews of similar quality, the most recent review was included.

Appendix 2

Full search string

('long-term' OR 'longer-term') AND ('treatment' OR 'intervention' OR 'therapy' OR 'secondary prevention' OR 'medication' OR 'pharmacother*' OR 'antidepressant*' OR 'methylphenidate' OR 'stimulant*') AND ('mental disorder*' OR 'psychiatr*' OR 'psychopathology' OR 'attention deficit hyperactivity disorder' OR 'ADHD' OR 'anxiety disorder*' OR depress* OR 'mood disorder*' OR 'phobia' OR 'impulse control disorder*' OR 'behavior disorder*' OR 'externalizing disorder*' OR 'internalizing disorder*') AND ('child*' OR 'youth' OR 'primary school' OR 'pupil') NOT ('autism' OR 'psychosis' OR 'schizophren*' OR 'dementia' OR 'bipolar' OR 'borderline personality disorder' OR 'eating disorder' OR 'obsessive compulsive disorder' OR 'obesity' OR 'anorexia' OR 'bulimia' OR 'binge eating disorder' OR 'cardi*' OR 'disease' OR 'syndrome' OR 'suicid*' OR 'speech' OR 'sleep*' OR 'epilep*' OR 'migraine' OR 'postmenopausal' OR 'pregnan*' OR 'postnatal' OR 'perinatal' OR 'postpartum' OR 'cancer' OR 'infan*' OR 'toddlers' OR 'preschool').

Filters: review, systematic review, meta-analysis, English, Dutch.

Accepted for publication: 17 June 2022