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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Agency for Healthcare Research and Quality

Supplemental Evidence and Data Request on Depression in Children: Systematic Review

AGENCY: Agency for Healthcare Research and Quality (AHRQ), HHS.

ACTION: Request for Supplemental Evidence and Data Submissions

SUMMARY: The Agency for Healthcare Research and Quality (AHRQ) is seeking scientific information submissions from the public. Scientific information is being solicited to inform our review of *Depression in Children: Systematic Review,* which is currently being conducted by the AHRQ's Evidence-based Practice Centers (EPC) Program. Access to published and unpublished pertinent scientific information will improve the quality of this review.

DATES: *Submission Deadline* on or before [**INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER**].

ADDRESSES:

E-mail submissions: epc@ahrq.hhs.gov.

Print submissions:

Mailing Address:

Center for Evidence and Practice Improvement

Agency for Healthcare Research and Quality

ATTN: EPC SEADs Coordinator

5600 Fishers Lane

Mail Stop 06E53A

Rockville, MD 20857

Shipping Address (FedEx, UPS, etc.):

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5600 Fishers Lane

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FOR FURTHER INFORMATION CONTACT:

Jenae Benns, Telephone: 301-427-1496 or Email: epc@ahrq.hhs.gov.

SUPPLEMENTARY INFORMATION:

The Agency for Healthcare Research and Quality has commissioned the Evidence-based Practice Centers (EPC) Program to complete a review of the evidence for *Depression in Children: Systematic Review.* AHRQ is conducting this systematic review pursuant to Section 902(a) of the Public Health Service Act, 42 U.S.C. 299a(a).

The EPC Program is dedicated to identifying as many studies as possible that are relevant to the questions for each of its reviews. In order to do so, we are supplementing the usual manual and electronic database searches of the literature by

requesting information from the public (e.g., details of studies conducted). We are looking for studies that report on *Depression in Children: Systematic Review*, including those that describe adverse events. The entire research protocol, including the key questions, is also available online at:

https://effectivehealthcare.ahrq.gov/topic/childhood-depression/protocol

This is to notify the public that the EPC Program would find the following information on *Depression in Children: Systematic Review* helpful:

- A list of completed studies that your organization has sponsored for this indication. In the list, please *indicate whether results are available on ClinicalTrials.gov along with the ClinicalTrials.gov trial number*.
    - *For completed studies that do not have results on ClinicalTrials.gov*, please provide a summary, including the following elements: study number, study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, primary and secondary outcomes, baseline characteristics, number of patients screened /eligible /enrolled /lost to follow-up /withdrawn /analyzed, effectiveness/efficacy, and safety results.
- *A list of ongoing studies that your organization has sponsored for this indication*. In the list, please provide the ClinicalTrials.gov trial number or, if the trial is not registered, the protocol for the study including a study number, the study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, and primary and secondary outcomes.

- Description of whether the above studies constitute ALL Phase II and above clinical trials sponsored by your organization for this indication and an index outlining the relevant information in each submitted file.

Your contribution will be very beneficial to the EPC Program. Materials submitted must be publicly available or able to be made public. Materials that are considered confidential; marketing materials; study types not included in the review; or information on indications not included in the review cannot be used by the EPC Program. This is a voluntary request for information, and all costs for complying with this request must be borne by the submitter.

The draft of this review will be posted on AHRQ's EPC Program website and available for public comment for a period of 4 weeks. If you would like to be notified when the draft is posted, please sign up for the e-mail list at: https://www.effectivehealthcare.ahrq.gov/email-updates.

The systematic review will answer the following questions. This information is provided as background. AHRQ is not requesting that the public provide answers to these questions.

The Key Questions (KQs)

1a. In adolescents and children, what are the benefits and harms of nonpharmacological interventions for depressive disorders (defined as MDD or PDD/DD)?

1b. How do these benefits and harms vary by subpopulation (e.g., patient characteristics, parent/caregiver characteristics, disorder characteristics,

history of previous treatment, comorbid condition, exposure to a traumatic life event)?

2a. In adolescents and children, what are the benefits and harms of pharmacological interventions for depressive disorders (defined as MDD or PDD/DD)?

2b. How do the benefits and harms vary by subpopulation (e.g., patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event?

3a. In adolescents and children, what are the benefits and harms of combination interventions for depressive disorders (defined as MDD or PDD/DD)?

3b. How do the benefits and harms vary by subpopulation (e.g., patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?

4a: In adolescents and children, what are the benefits and harms of collaborative care interventions for depressive disorders (defined as MDD or PDD/DD)?

4b: How do the benefits and harms vary by subpopulation (e.g., patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?

5a: In adolescents and children, what are the comparative benefits and harms of treatments (pharmacological, nonpharmacological, combined, collaborative care interventions) for depressive disorders (defined as MDD or PDD/DD)?

5b. How do these benefits and harms vary by subpopulation (e.g., patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Settings)

Table 1. PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Settings) and Inclusion/exclusion criteria

PICOTS	**Inclusion**	**Exclusion**
Population	Children and adolescents (≤18 years old) with a depressive disorder (MDD or PDD/DD) as indicated by a diagnosis made from an established taxonomy (e.g., DSM, ICD) via administration of a structured or semi-structured clinical interview (CIDI, DISC, SCID, PRIME-MD, Kinder-DIPS, K-SADS, DICA, CAS, SADS, DAWBA, SCAN), use of a cutpoint indicative of clinical MDD or PDD/DD as measured by a clinically validated depression scale (BDI, CDI, CESD, PHQ, MFQ, ChilD-S),* or via a clinician diagnosis Subgroups of interest (KQs 1b, 2b, 3b, 4b, 5b) include those distinguished by patient characteristics (e.g., developmental age—child or adolescent, gender, race/ethnicity), parent/caregiver characteristics, disorder characteristics (e.g., type, severity), history of previous treatment, comorbid condition, and exposure to a traumatic life event	All other children and adolescents (≤18 years old); all adults >18 years old.

Table 1. PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Settings) and Inclusion/exclusion criteria (continued)

PICOTS	**Inclusion**	**Exclusion**
Intervention	**Nonpharmacological interventions**: Psychological/psychosocial: Cognitive behavioral therapy, rational emotive behavior therapy, behavioral activation, other behavioral therapy, interpersonal therapy, directive counseling, Katathym-imaginative Psychotherapy, family therapy, parent education, self-help groups, problem-solving therapy, autonomic training, combined-modality therapy, psychological adaptation therapies Lifestyle: Exercise (physical activity), diet therapy, mindfulness (including mindfulness-based stress reduction), meditation (including mindfulness mediation), relaxation therapy, massage therapy, music therapy, art therapy, integrative restoration, visualization, tai-chi, yoga, spirituality, acupuncture Supplements: St. John's Wort, SAMe, fish oil, melatonin, L-tryptophan, folic acid, 5-HTP, zinc, chromium, gingko biloba, vitamin E, omega-3 fatty acids, hypericum, inositol, selenium Other: Electroconvulsive therapy, transcranial magnetic stimulation, light therapy (phototherapy), hypnotherapy (including self-hypnotherapy), neurofeedback, deep brain stimulation, biofeedback	All other interventions

	Pharmacological interventions: Selective serotonin reuptake inhibitors (SSRIs): Citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, vilazodone Serotonin and norepinephrine reuptake inhibitors (SNRIs): Duloxetine, venlafaxine Tricyclic antidepressants: *Amitriptyline*, desipramine, imipramine, nortriptyline, doxepin, c*lomipramine* Monoamine oxidase inhibitors: *Rasagiline, selegiline, isocarboxazid, phenelzine, tranylcypromine* Atypical antidepressants: Bupropion, mirtazapine, nefazodone, trazodone, vortioxetine **Combination interventions**: Any combined treatment that includes two or more types of nonpharmacological, pharmacological, and/or collaborative care interventions, either started together or given as augments to initial treatment types	
	Collaborative care interventions: Collaborative care, integrated care, integrative care, stepped care, coordinated care, co-managed care, co-located care	

Table 1. PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Settings) and Inclusion/exclusion criteria (continued)

PICOTS	Inclusion	Exclusion
Comparator	KQ 1: Treatment as usual, sham, attention control, wait list control KQ 2: Placebo, treatment as usual, attention control, wait list control KQ 3: Treatment as usual, placebo, sham, attention control, wait list control KQ 4: Treatment as usual, placebo, sham, attention control, wait list control KQ 5: Any nonpharmacologic, pharmacologic, or collaborative care intervention alone or in combination	All other comparators
Outcomes****	Benefits: Remission Response Relapse Depressive symptoms Suicidality Mortality Functional impairment Harms: Any AEs of intervention (e.g., death, serious adverse events)	All other outcomes
Time frame	Any publication dates At least 6 weeks of treatment	Less than 6 weeks of treatment

Settings	Outpatient care in countries with a very high Human Development Index**	Inpatient care, studies conducted in countries without a very high Human Development Index
Study design	For benefits: • Adolescents (sample age >12 and ≤18): randomized controlled trials (RCTs) • Children (sample age ≤12): RCTs or controlled clinical trials (CCTs) For harms: • RCTs, CCTs, and observational studies*** Reference lists of relevant systematic reviews published in 2013 or later will be used to ensure our search strategies captured all relevant studies.	All other designs and studies using included designs that do not meet the sample size criterion
Language	Studies published in English	Studies published in languages other than English

* In the absence of clear, clinically validated cutoffs of depression scales used to indicate a either MDD or PDD/DD, the research team will consult two recent systematic reviews [1, 2] on the topic and discuss required thresholds with the Technical Expert Panel (TEP) for each scale.

** http://hdr.undp.org/en/content/human-development-index-hdi

*** The research team will evaluate the yield for harms. When studies with sample sizes of 1,000 or more participants are available for a given intervention and comparator, the team plans to restrict the analysis to that group. If large samples are not available, the team plans to include studies with smaller sample sizes

****The research team anticipates grading all outcomes but if needed (based on the volume of evidence), they may seek input from the TEP on prioritizing outcomes for strength of evidence grading.

AE = adverse event; BDI = Beck Depression Inventory; CAS: The Child Assessment Schedule; CBT = cognitive behavioral therapy; CCT = controlled clinical trial; CIDI = Composite International Diagnostic Interview; CDI = Children's Depression Inventory; CES-D = Center for Epidemiological Studies Depression Scale; ChilD-S: Children's Depression Screener; DAWBA = The Development and Wellbeing Assessment; DD = dysthymic disorder; DICA = Diagnostic Interview for Children and Adolescents; DISC = Diagnostic Interview Schedule for Children; DSM = *Diagnostic and Statistical Manual*; IPT = interpersonal therapy; Kinder-DIPS = The Diagnostic Interview for Psychiatric Disorders in Children and Adolescents; K-SADS = The Schedule for Affective Disorders and Schizophrenia for School-Age Children; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; PDD = persistent depressive disorder; PHQ = Patient Health Questionnaire; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; PRIME-MD = The Primary Care Evaluation of Mental Disorders; RCT = randomized controlled trial; SADS = The Schedule for Affective Disorders and Schizophrenia; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; SCID = Structured Clinical Interview for DSM disorders.

References:

1. Roseman M, Kloda LA, Saadat N, et al. Accuracy of Depression Screening Tools to Detect Major Depression in Children and Adolescents: A Systematic Review. Can J Psychiatry. 2016 Dec;61(12):746-57. doi: 10.1177/0706743716651833. PMID: 27310247.
2. Stockings E, Degenhardt L, Lee YY, et al. Symptom screening scales for detecting major depressive disorder in children and adolescents: a systematic review and meta-analysis of reliability, validity and diagnostic utility. J Affect Disord. 2015 Mar 15;174:447-63. doi: 10.1016/j.jad.2014.11.061. PMID: 25553406.

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