Evidence-based Practice Center Systematic Review Protocol

Project Title: *Depression in Children: Systematic Review*

I. Background and Objectives for the Systematic Review

Depression among children and adolescents is a major public health problem associated with other mental and physical health conditions, poor functional impairment, and increased risk of early mortality from suicide.[1-6] The current version of the *Diagnostic and Statistical Manual* (DSM-5)[7] includes two main types of depression diagnoses applicable to children and adolescents: major depressive disorder (MDD) and persistent depressive disorder (PDD), formerly called dysthymic disorder (DD) in DSM-IV.[8] As shown in Table 1, these depressive disorders share a number of characteristics, although PDD tends to be longer-lasting, but often times less acutely impairing, than MDD. One nationally representative estimate indicated that about 1 in 12 (8-9 %) adolescents ages 13 to 17 years had a clinically significant depressive disorder (MDD or PDD) in the past year.[9] Although estimates for children younger than 12 or 13 (henceforth referenced as "younger children") have been less well studied, one review found an aggregated estimate of 2.8 percent of children under 13 had a formal diagnosis of a depressive disorder (MDD or PDD) using an established taxonomy and a structured or semi-structured psychiatric interview of adequate reliability.[10] Research has demonstrated that the onset of depressive disorders prior to age 18 may lead to long-term negative sequelae lasting into adulthood, including suicidality, co-occurring mental, substance, and physical health disorders, decreased social and academic functioning, and relationship problems.[11-13] The potential for lasting negative effects of child-onset depression underscores the importance of its early identification, diagnosis, and subsequent treatment. [9] Despite evidence that there are several effective treatments for depression, one 2016 national survey indicated that only 40.9 percent of adolescents 12 to17 years of age who experienced a major depressive episode in the prior 12 months reported receiving depression treatment during the same time period.[14] Several nonpharmacologic and pharmacologic interventions used to treat child and adolescent depression are described below.

Source: www.effectivehealthcare.ahrq.gov
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Table 1. DSM-5 criteria for MDD and PDD

Condition	Criteria
Major depressive disorder	At least 5 of the following 9 symptoms during a same 2-week period (with at least one symptom being either depressed or irritable mood or anhedonia) 1. Depressed or irritable mood 2. Decreased interest or lack of enjoyment 3. Decreased concentration or indecision 4. Insomnia or hypersomnia 5. Change of appetite or change of weight 6. Excessive fatigue 7. Feelings of worthlessness or excessive guilt 8. Recurrent thoughts of death or suicidal ideation 9. Psychomotor agitation or retardation. • Symptoms cause significant distress or impairment in social, occupational, or other important areas of functioning • Symptoms not attributed to the physiological effects of a substance or another medical condition • No lifetime manic or hypomanic episode • Symptoms are not better explained by schizoaffective disorder or other psychotic disorder.
Persistent depressive disorder (dysthymic disorder)	• At least 3 of the following 7 symptoms that occur most of the day, more days than not, for at least 1 year (with sad or irritable mood as one of the symptoms), with no more than 2 months at a time absent of the criteria during the year 1. Sad or irritable mood 2. Increased or decreased appetite 3. Insomnia or hypersomnia 4. Fatigue 5. Decreased self-esteem 6. Poor concentration or indecision 7. Feelings of hopelessness. • Symptoms cause significant distress or impairment in multiple areas of functioning • Symptoms not attributed to the physiological effects of a substance or another medical condition • No lifetime manic or hypomanic episode • Symptoms not better explained by schizoaffective disorder or other psychotic disorder.

Source: American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Nonpharmacological Interventions

Several nonpharmacological interventions are widely used to treat childhood depression (see Table 2). These interventions include different types of psychotherapies, educational therapies, and brain stimulation therapies.[15-18] Existing treatments vary greatly in the number of trials testing efficacy, effectiveness, and associated adverse events (AEs); that is, some interventions

have been tested extensively, whereas others have scant evidence supporting the potential benefits and harms associated with their use.

Table 2. Nonpharmacological interventions used to treat child and adolescent depression

Intervention Type	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

Trials testing efficacy and effectiveness differ by numerous factors: types of symptoms experienced and severity of depression, coexisting conditions among those in the samples, intervention components, comparators (e.g., other nonpharmacological interventions, pharmacological treatments, inactive comparators), outcomes tested, length of interventions, time frames for outcome assessments, and settings. Few trials explore subgroup variation in benefits and harms. Long-term outcomes of these interventions remain largely unknown; some trials do not report any follow-up assessments and very few report those longer than 12 months post intervention. As a result, the evidence base is inconsistent, as demonstrated in differences in findings across various recent systematic reviews (SRs).[19-26] Finally, the evidence base is much weaker for younger children than for adolescents; at least some interventions may differ in efficacy or effectiveness between adolescents and younger children.[27]

Although some evidence exists for benefits, particularly from nonpharmacological treatments, very few studies report associated harms. The 2013 review published for the U.S. Preventive Services Task Force (USPSTF) recommendation on screening for MDD among children and adolescents in primary care indicated that, with one exception (the Treatment for Adolescents with Depression Study,[28] which also included two groups who received a pharmacological treatment), no psychotherapy intervention efficacy trial reported harms as an outcome. The absence of information on harms associated with nonpharmacological interventions precludes making an informed recommendation that adequately weighs the benefits and harms of these treatments.

Pharmacological Interventions

Several pharmacotherapies are used to treat child and adolescent depression (see Table 3). Findings from pharmacological trials have been mixed and primarily focused on adolescents. Currently, two types of selective serotonin reuptake inhibitors (SSRIs) have been approved by the Food and Drug Administration (FDA) to treat MDD: fluoxetine for children ages 8 or older and escitalopram for adolescents ages 12 to 17. Thus, the FDA has not approved any medications

to treat depression in children less than 8 years old. Some health practitioners prescribe other SSRIs (e.g., citalopram, sertraline, fluvoxamine), other second-generation antidepressants (including serotonin and norepinephrine reuptake inhibitors [SNRIs], such as venlafaxine, duloxetine), or older medications such as tricyclic antidepressants[29] to depressed children and adolescents on an off-label basis.

Table 3. Pharmacological agents used to treat child and adolescent depression

Class	Drugs
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, vilazodone
Serotonin and norepinephrine reuptake inhibitors (SNRIs)	Duloxetine, venlafaxine
Tricyclic antidepressants (TCAs)	Amitriptyline, desipramine, imipramine, nortriptyline, doxepin, clomipramine
Monoamine oxidase inhibitors (MAOIs)	Rasagiline, selegiline, isocarboxazid, phenelzine, tranylcypromine
Atypical antidepressants	Bupropion, mirtazapine, nefazodone, trazodone, vortioxetine

Use of SSRIs in children has been a substantial concern over the years. In 2003, FDA published a recommendation for clinicians to stop prescribing one SSRI, paroxetine, for children and adolescents younger than 18 years old because of reports of possible increased risk of suicidal ideation and suicide attempts. In the following year, FDA issued a public warning about the possibility of increased risk of suicidality in some children and adolescents treated with antidepressants. A subsequent review of pediatric depression trials conducted between 1986 and 2006 concluded, however, that the benefits of antidepressant medications likely outweigh their potential risks for suicidal ideation and attempts.[30] Although the widespread use of paroxetine has declined, concerns remain regarding the risk of suicidality. Currently, FDA requires a boxed warning on these medications about the potential danger of suicidality with a recommendation to closely monitor for worsening of depression, agitation or withdrawal, and increased suicidal thoughts or behaviors. The last SR for USPSTF to inform recommendations for screening for pediatric depression did not include paroxetine in the review; it found no evidence of significant harms from placebo-controlled trials of other pharmacotherapies used to treat childhood MDD. Because pooled studies were inadequately powered, the review cautioned against interpreting a lack of findings about AEs as proof that pharmacotherapies pose no risk of harms. Examining gray literature for unpublished studies of harms might enable a broader consideration of benefits and harms for specific medications.

For PDD, FDA has not approved any medications for children. American Academy of Child and Adolescent Psychiatry (AACAP)[31] recommends that interventions proven efficacious or effective in treating MDD in children and adolescents be used for those with PDD. The applicability of MDD treatments to pediatric patients with PDD, however, remains largely unknown. Most prior studies that included children and adolescents with different types of depressive disorders such as MDD and PDD have not presented findings stratified by depressive disorder type.

Combination Interventions

Combination interventions include the use of two or more intervention types. The interventions can be two or more different types of nonpharmacotherapy (e.g., CBT and exercise), two or more

different types of pharmacotherapy (e.g., fluoxetine and trazodone), or two or more types of treatments that span both nonpharmacotherapy and pharmacotherapy (e.g., fluoxetine and CBT). The different interventions may be started concurrently or staggered (e.g., one treatment followed by another new intervention 4 weeks later). Several of the combined psychotherapy and pharmacotherapy interventions have shown greater improvements following combination treatment than with either psychotherapy or pharmacotherapy alone in studies conducted on children and adolescents.[32-34]

Collaborative Care

Collaborative care is a method used to deliver both pharmacological and nonpharmacological interventions delivered by a healthcare team. Similar interventions focused on a team providing coordinated care may be referenced as co-managed care, co-located care, integrated care, integrative care, and stepped care. The delivery of these types of interventions require a change to the system in which depression care is delivered. Frequently, primary care providers and mental health specialists work together to deliver collaborative care interventions with the support of a case manager to identify and treat patients in need. There has been growing research in evaluating collaborative care interventions used to treat patients with depression; several studies demonstrate improved outcomes,[35] and some indicate potential efficacy among children and adolescents, specifically.[36, 37]

Comparative Effectiveness

Few comparative effectiveness studies of treatments for childhood depression[38] have been conducted. Identifying differences in the comparative effectiveness of therapies would allow clinicians to tailor interventions to individual patients to optimize benefits and minimize harms.

Depression Outcomes

Studies testing the efficacy or effectiveness of depression interventions among children or adolescents typically include at least one depression-related outcome, such as reduction in depressive symptoms, remission (typically defined as a continuous measure of depression decreasing below a prespecified level or percentage of initial score), response, loss of diagnosis, or, in studies testing longer-term outcomes, relapse of depressive disorder. Other important outcomes include a reduction in suicidality (thoughts, plans, or attempts), mortality, and functional impairment.

Outcomes measuring harms are also important to consider. In addition to overall and specific AEs such as disturbed sleep, increased agitation, sedation, weight gain, sleep issues, gastrointestinal difficulties, appetite changes, manic behavior, metabolic side effects, suicidality, and mortality, withdrawals due to AEs should be considered. The sequelae of untreated depression also can be considered an important harm.

Subpopulations

The efficacy and effectiveness of child and adolescent depression interventions may vary by a few subpopulation characteristics. Most notably, the developmental age of the sample (adolescent vs. younger children) is a critical component when considering potential differences.

As such, separate examinations of benefits and harms among children and adolescents are recommended when possible. Other key subpopulation characteristics that might affect differential efficacy include depression severity, depression chronicity (first episode vs. recurrent), comorbid conditions, exposure to a traumatic life event, and treatment phase (acute, continuation, maintenance). In addition to these and other patient characteristics, efficacy might differ by intervention characteristics, mode of delivery of intervention, location of treatment, and adherence to the intervention being tested.

Summary of Existing Clinical Practice Guidelines

Several guidelines for the treatment of child and adolescent depression, including details on the scope and applicability, are described in Table 4. In sum, most guidelines recommend treatment type depending on level of severity (mild, moderate, severe). Across guidelines, either active support and monitoring or psychotherapy are recommended for patients with mild depressive disorders, whereas SSRI medications or a combination of psychotherapy and SSRIs is recommended for patients with moderate or severe disorders (as well as those with mild disorders who do not improve).The National Institute for Health and Care Excellence (NICE) guideline suggests that patients with at least moderate levels of depression severity may benefit from starting psychotherapy and SSRI concurrently. In addition, little evidence of the superiority of one treatment over another exists. All guidelines suggest active monitoring for potential adverse events and ensuring that the treatment phase lasts for an adequate amount of time.

Clinical Uncertainties

Clinicians contend with numerous challenges in treating childhood depression appropriately. Perhaps most importantly, clinicians need to account for developmental changes over the course of childhood and adolescence that likely have widespread impacts on outcomes. Adolescents and younger children may experience differential benefits and harms depending on treatment type.[39] In addition, differences in outcomes may vary by severity and type of depressive disorder (e.g., MDD vs. PDD). Although the evidence on PDD is relatively sparse, PDD can be a gateway to MDD and signal high risk of recurrent mood disorders. Other clinical uncertainty persists regarding how the harms may vary according to dose of medication or how the efficacy of treatments vary by frequency of intensity of the nonpharmacological intervention. These uncertainties obscure best practices in selecting a treatment most likely to benefit each individual patient.

Finally, few nonpharmacological studies have systematically collected and reported harms data (e.g., re-experiencing trauma, suicidality),[40] which leads to uncertainty about weighing the risks and benefits of different types of treatment. Information on AEs that comes from passive surveillance of spontaneous reporting may not be comprehensive; additionally, selection bias and confounding may complicate the interpretation of findings from these sources

Rationale for the Review and Objectives

The current review is urgently needed to help answer some of the uncertainties surrounding age-specific and disorder-specific best practices for treatment of child and adolescent depressive disorders. For example, better information on PDD treatment might help clinicians resolve

depressive symptoms in these young patients, reduce their risk of developing other mood disorders, strengthen psychosocial functioning, and prevent or reduce serious long-term sequelae.

The review will use rigorous methods to compile the evidence base and synthesize the findings to identify the most efficacious treatments, potential harms, subpopulations that might benefit from a treatment type, and gaps in the field that may require additional research.

Table 4. Current clinical practice guidelines for the treatment of child and adolescent depressive disorders

Guideline (year of publication)	Process Used to Produce Guideline	Population	Treatment Recommendations
GLAD-PC, 2018[41, 42] (supported by AAP and CPS)	SRs, expert consensus, input from youth and families with lived experience	Patient: Adolescents ages 10-21 with MDD differentiated by severity level (mild, moderate, severe) *	Active support and monitoring for 6-8 weeks for patients with mild MDD; referral to mental health specialists for patients with moderate to severe MDD and those who do not improve with active support and monitoring. Advocates for the use of psychotherapies (CBT or interpersonal therapy [IPT]), SSRI medications, or both.
USPSTF, 2016[43]	SRs, expert consensus	Adolescents with MDD (insufficient evidence to make a recommendation for children)	Guideline did not state explicit treatment recommendations because it focuses on screening for depression in pediatric primary care settings; however, part of the chain of indirect evidence used to make the recommendation included efficacy of CBT, collaborative care, fluoxetine, CBT+fluoxetine, and escitalopram among adolescents.
NICE, 2015[44]	SR and consideration of cost-effectiveness	Children and adolescents with depression (unspecified type), with recommendations made according to severity	Several psychological therapies have shown efficacy, with no clear evidence of superiority of one over another in comparative effectiveness studies; adolescents with depression of at least moderate severity may benefit from starting psychological and pharmacotherapy concurrently; antidepressants are not recommended for adolescents with mild depression; when pharmacotherapy is indicated, the guidelines call for vigilant, active monitoring for adverse drug reactions.
AACAP, 2007[45]	Rigorous review of empirical evidence and clinical consensus	Children and adolescents with depressive disorders (unspecified), with recommendations varying by severity, duration, history of prior depressive episodes, and complications	Depression of short duration with no complications or with mild impairment can be treated with education, support, and case management; nonresponse to these initial strategies or those with complicated or depression symptoms accompanied by moderate to severe functional impairment should be followed by a trial of psychotherapy or antidepressants; treatment should be continued for 6-12 months and, to prevent recurrence, longer if possible for some youth who might have a history of relapse/recurrence after treatment, chronic or severe types of depression, or long prior periods of recovery.

*Authors mention that recommendations can be applied to adolescents with PDD and premenstrual dysphoric disorder as well.

AACAP = American Academy of Child and Adolescent Psychiatry; AAP = American Academy of Pediatrics; CBT = cognitive behavioral therapy; CPS = Canadian Pediatric Society; GLAD-PC = Guidelines for Adolescent Depression in Primary Care; IPT = interpersonal therapy; MDD = major depressive disorder; NICE = National Institute for Health and Care Excellence; SR = systematic review; SSRI = selective serotonin reuptake inhibitor; USPSTF = United States Preventive Services Task Force.

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II. The Key Questions

The original set of Key Questions (KQs) included questions focused on children and adolescents with MDD and PDD, separately. The updated KQs include the term "depressive disorders" instead of separate MDD and PDD focus because that will allow the data to be synthesized together or, if suitable, stratified by disorder type. The change will allow for the inclusion of studies focused on children and adolescents with different types of depressive disorders.

Revised Key Questions

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

KQ 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)?

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

KQ 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?

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

KQ 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)?

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

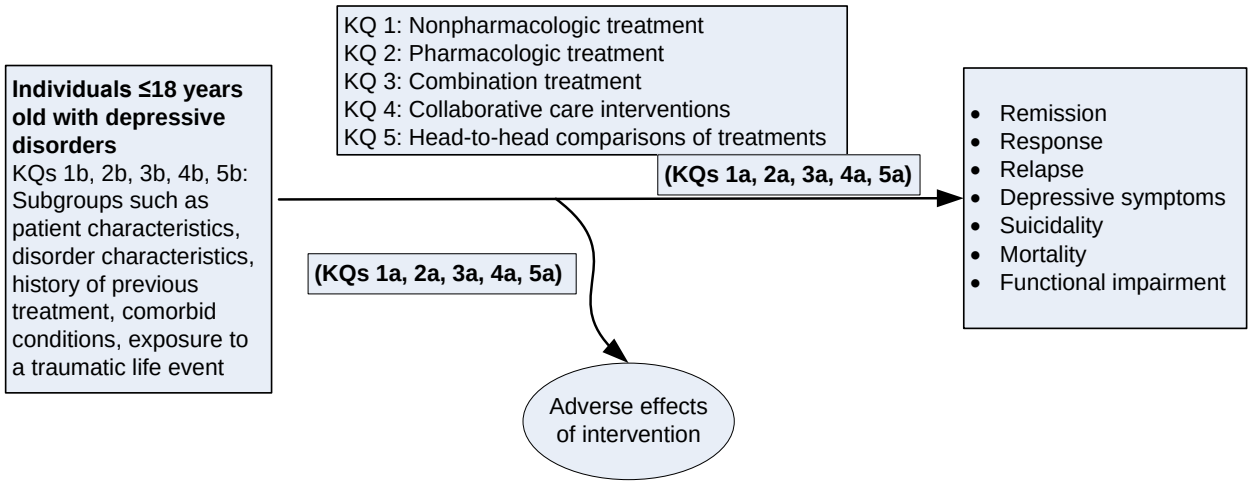
KQ 4b: How do the benefits and harms vary by subpopulation (e.g., patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?

KQ 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)?

KQ 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)?

III. Analytic Framework

Figure 1. Analytic Framework for Depression in Children



KQ = Key Question.

Figure 1: This figure depicts the KQs within the context of the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) for childhood/adolescent depressive disorders (defined as MDD or PDD/DD). The figure illustrates how pharmacologic and/or nonpharmacologic treatments and/or collaborative care interventions, versus other treatments or controls for depressive disorder and patient subgroups, may result in final health outcomes (such as remission, response, relapse, depressive symptoms, suicidality, mortality, and functional impairment). Adverse events may occur at any point after the treatment is received.

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

The revised criteria for the inclusion/exclusion are listed in Table 5.

Table 5. 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.
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

PICOTS	Inclusion	Exclusion
	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, clomipramine 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 5. 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, we will consult two recent systematic reviews[46, 47] on the topic and discuss required thresholds with our Technical Expert Panel (TEP) for each scale.

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

*** We 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, we plan to restrict the analysis to that group. If large samples are not available, we plan to include studies with smaller sample sizes

****We anticipate grading all outcomes but if needed (based on the volume of evidence), we 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; KQ = Key Question; 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.

Searching for the Evidence:

Literature Search Strategies

We will systematically search, review, and analyze the scientific evidence for each KQ.

To identify articles relevant to each KQ, we will begin with a focused MEDLINE search using a variety of terms, medical subject headings (MeSH), and major headings and will limit the search to English-language and human-only studies. We list relevant terms to include in Appendix B. We will also search the Cochrane Library, the Cochrane Central Trials Registry, the Cumulative Index to Nursing and Allied Health Literature, and PsycINFO by using analogous search terms. We will conduct quality checks to ensure our search identifies known studies. If not, we will revise and rerun our searches. We do not plan to impose a limit on publication date. An experienced librarian familiar with systematic reviews will design and conduct all searches in consultation with the review team. We will search the gray literature for unpublished studies relevant to this review and will include studies that meet all the inclusion criteria and contain enough methodological information for assessing internal validity/quality. Sources of gray literature include ClinicalTrials.gov, pharmaceutical companies' dossiers (for pharmacotherapies of interest), and scientific evidence and, if applicable, data received in response to *Federal Register* notice requests.

We will also conduct an updated literature search (of the same databases searched initially) concurrent with the draft report peer/public review process. We will investigate any literature the peer reviewers or the public suggest and, if appropriate, will incorporate them into the final review. We will identify all eligible studies using the same criteria described above. For the studies that address the subgroup KQs (KQs 1b, 2b, 3b, 4b, 5b), we will include only studies that directly compare the efficacy or effectiveness between subgroups of interest.

Data Abstraction and Data Management

Two trained research team members will independently review all titles and abstracts identified through searches for eligibility against our inclusion/exclusion criteria using Abstrackr.[48] Studies marked for possible inclusion by either reviewer will undergo a full-text review. For studies without adequate information to determine inclusion or exclusion, we will retrieve the full text and then make the determination. All results will be tracked in an EndNote® bibliographic database (Thomson Reuters, New York, NY).

We will retrieve and review the full text of all titles included during the title/abstract review phase. Two trained team members will independently review each full-text article for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agree that a study does not meet the eligibility criteria, the study will be excluded. If the reviewers disagree, conflicts will be resolved by discussion and consensus or by consulting a third member of the review team. As described above, all results will be tracked in an EndNote database. We will record the reason why each excluded full text did not satisfy the eligibility criteria so that we can later compile a comprehensive list of such studies.

For studies that meet our inclusion criteria, we will abstract relevant information into a table displaying study characteristics. We will design data abstraction forms to gather pertinent information from each article, including characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers will extract the relevant data from each included article into the evidence tables. A second member of the team will review all data abstractions for completeness and accuracy.

Assessment of Methodological Risk of Bias of Individual Studies

We will use the criteria set forth by the Agency for Healthcare Quality and Research's (AHRQ's) *Methods Guide for Comparative Effectiveness Reviews*. To assess the risk of bias (i.e., internal validity) we will use the ROBINS-1[49] tool for observational studies and the Cochrane RCT tool[50] for RCTs. For both RCTs and observational studies, risk of bias assessment will include questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias; concepts covered include those about adequacy of randomization (for RCTs only), similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity.[51]

Two independent reviewers will assign risk of bias ratings for each study. Disagreements between the two reviewers will be resolved by discussion and consensus or by consulting a third member of the team. We will give a low risk of bias rating to studies that meet all criteria. Studies that do not report their methods sufficiently may be rated as unclear risk of bias. We will give a high risk of bias rating to studies that have a methodological shortcoming that leads to a very high risk of bias, in one or more categories, and will exclude them from our main analyses.

Data Synthesis

We will summarize all included studies in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, outcomes, setting (including geographic location), and results. Besides mention of basic study characteristics, we will include only findings from studies of low, medium. or unclear risk of bias in our main report, synthesized either qualitatively or quantitatively as permitted. Findings from studies determined to be of high risk of bias will be listed in the evidence tables in the appendix. If feasible, qualitative or quantitative sensitivity analyses may be conducted to gauge the difference in conclusions upon including and excluding high risk of bias studies.

If we find three or more studies for a comparison of a outcome of interest, we will consider pooling our findings by using quantitative analysis (i.e., meta-analysis) of the data from those

studies. We will also consider conducting network meta-analysis using Bayesian methods to compare the interventions with each other if we identify at least three studies that tested the same intervention with a common comparator (e.g., placebo). For all analyses, we will use random effects models to estimate pooled or comparative effects; unlike a fixed-effects model, this approach allows for the likelihood that the true population effect may vary from study to study. To determine whether quantitative analyses are appropriate, we will assess the clinical and methodological heterogeneity of the studies under consideration following established guidance.[52]

If we conduct quantitative syntheses (i.e., meta-analysis), we will assess statistical heterogeneity in effects between studies by calculating the chi-squared statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity). The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence (SOE) for heterogeneity (e.g., p-value from the chi-squared test or a confidence interval for I^2). If we include any meta-analyses with considerable statistical heterogeneity in this report, we will provide an explanation for doing so, considering the magnitude and direction of effects.

When possible, for each intervention/comparator grouping, we will present findings clustered by age of sample (adolescents with those 13 years or older, children with those ≤12 years, mixed samples). In addition, to examine potential sources of heterogeneity, we will use meta-regression or subgroup analyses to examine effect sizes by depression characteristics (MDD, PDD, mixed types, treatment-resistant depression, level of severity, comorbidity, or exposure to a traumatic life event), patient characteristics (e.g., gender, race/ethnicity), and intervention characteristics (mode of delivery, including technology-based delivery) as permitted by the number of studies that have similar interventions, comparators, outcomes, and timing of assessments. When quantitative analyses are not appropriate (e.g., due to heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we will synthesize the data qualitatively.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We will grade the SOE based on the guidance established for the Evidence-based Practice Center (EPC) Program.[53] Developed to grade the overall strength of a body of evidence, this approach incorporates five key domains: risk of bias (includes study design and aggregate quality), consistency, directness, precision of the evidence, and reporting bias. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect).

Table 6 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer KQs on the comparative effectiveness, efficacy, and harms of the interventions included in this review. Two reviewers will assess each domain for each key outcome, and differences will be resolved by consensus. If the volume of evidence is large, we may focus the SOE for the outcomes deemed to be of greatest importance to decisionmakers and those most commonly reported in the literature. Based on input thus far from key informants, we expect these to include depression symptom reduction, remission, relapse, recovery, suicidality, and AEs.

Table 6. Definitions of the grades of overall SOE[54]

Grade	**Definition**
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

SOE = strength of evidence.

Assessing Applicability

We will assess the applicability of individual studies as well as the applicability of a body of evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[55] For individual studies, we will examine conditions that may limit applicability based on the PICOTS structure. Some factors identified a priori that may limit the applicability of evidence include the following: age of the sample (adolescent vs. younger children), comorbid conditions, exposure to a traumatic life event, severity or type of depressive disorder, history of previous depressive episodes or depression treatment, or setting (primary care vs. specialty care).

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VI. Definition of Terms

We will define important terms in the full report.

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below (Table 7):

Table 7. Example table

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as "because the AE/TOO/TEP/Peer reviewer told us to" but explain what the change hopes to accomplish.

VIII. Review of Key Questions

AHRQ posted the KQs on the AHRQ Effective Health Care Website for public comment. The EPC refined and finalized the KQs after reviewing the public comments and input from Key Informants and the Technical Expert Panel. This input is intended to ensure that the KQs are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the KQs for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end users, individuals are invited to serve as Key Informants, and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and

identify studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts, and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer Reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer Reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $5,000. Peer Reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHSA290201500011I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Childhood Depression Final Searches published literature in PubMed/Medline, Cochrane Library, and PsycInfo, 7-25-18
1st addendum database - CINAHL done 7-27-18
2nd addendum in all indexes for rarely used drugs, done Aug 6-7, 2018

PubMed

Benefits:

Clinical Trials = 5459, all imported
Systematic Reviews = 631, 498 imported

Harms: 932, all imported

Systematic Reviews = 16
All other study designs = 916

Search	PubMed Query	Items found
#1	Search "Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH] OR Depression[MeSH] OR depress*[Title/Abstract] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed[Title/Abstract] OR "Dysthymic Disorder"[Mesh] OR dysthymia OR dysthymic OR "Persistent Depressive Disorder"[ALL FIELDS]	450239
#2	Search ("Antidepressive Agents, Second-Generation"[MeSH] OR "Serotonin Uptake Inhibitors"[MeSH] OR "Antidepressive Agents"[MeSH] OR antidepressant*[Title/Abstract] OR antidepressives[Title/Abstract] OR ("antidepressive agent"[Title/Abstract] OR "antidepressive agents"[Title/Abstract] OR "antidepressive drug"[Title/Abstract] OR "antidepressive drugs"[Title/Abstract] OR "selective serotonin reuptake inhibitor"[Title/Abstract] OR "selective serotonin reuptake inhibitors"[Title/Abstract]) OR ssri[Title/Abstract] OR ssris[Title/Abstract] OR Fluoxetine[MeSH] OR fluoxetine[Title/Abstract] OR "Vilazodone Hydrochloride"[Mesh] OR vilazodone[Title/Abstract] OR Prozac[Title/Abstract] OR Fluvoxamine[MeSH] OR Fluvoxamine[Title/Abstract] OR "mirtazapine" [Supplementary Concept] OR mirtazapine[Title/Abstract] OR "nefazodone"[Supplementary Concept] OR nefazodone[Title/Abstract] OR "Trazodone"[Mesh] OR trazodone[Title/Abstract] OR "vortioxetine"[Supplementary Concept] OR vortioxetine[Title/Abstract] OR luvox[Title/Abstract] OR Paroxetine[MeSH] OR paroxetine[Title/Abstract] OR paxil[Title/Abstract] OR Sertraline[MeSH] OR sertraline[Title/Abstract] OR Zoloft[Title/Abstract] OR Citalopram[MeSH] OR citalopram[Title/Abstract] OR celexa[Title/Abstract] OR escitalopram[Title/Abstract] OR Lexapro[Title/Abstract] OR "serotonin norepinephrine reuptake inhibitors"[All Fields] OR snri*[All Fields] OR "norepinephrine reuptake inhibitors"[all fields] OR venlafaxine[All Fields] OR duloxetine[All Fields] OR Bupropion[MeSH] OR Bupropion[All Fields])	107393
#3	Search (#1 and #2)	54003

Search	PubMed Query	Items found
#4	Search (Psychotherapy[MeSH] OR Psychotherapy, Brief[MeSH] OR Psychotherapy, Group[MeSH] OR psychotherapy*[Title/Abstract] OR Cognitive Therapy[MeSH] OR (cognitive[Title/Abstract] AND (therap*[Title/Abstract] OR treatment*[Title/Abstract] OR intervention*[Title/Abstract])) OR "Behavior Therapy"[MeSH] OR (behavior*[Title/Abstract] AND (therap*[Title/Abstract] OR treatment*[Title/Abstract] OR intervention*[Title/Abstract])) OR CBT[Title/Abstract] OR (interpersonal[Title/Abstract] AND therap*[Title/Abstract]) OR (interpersonal[Title/Abstract] AND intervention*[Title/Abstract]) OR IPT[Title/Abstract] OR e-health[Title/Abstract] OR ehealth[Title/Abstract] OR (Internet[tiab] AND health[tiab]) OR "behavioral activation"[Title/Abstract] OR "Delivery of Health Care, Integrated"[Mesh] OR "integrated care"[Title/Abstract] OR "integrative care"[Title/Abstract] OR "Self-Help Groups"[MeSH] OR "self help"[Title/Abstract] OR Family Therapy[MeSH] OR ("family support"[Title/Abstract]) OR (parent*[Title/Abstract] AND education[Title/Abstract]) OR Parents/education[MeSH] OR Counseling[MeSH] OR "Directive Counseling"[MeSH] OR counsel*[Title/Abstract] OR "Problem Solving"[MeSH] OR "problem solving"[Title/Abstract] OR "Adaptation, Psychological"[Mesh] OR "coping skills"[Title/Abstract] OR "Phototherapy"[Mesh] OR "light therapy"[Title/Abstract] OR phototherapy[Title/Abstract] OR "light therapies"[Title/Abstract])	790156
#5	Search (#1 and #4)	73801

Search	PubMed Query	Items found
#6	Search ("Deep Brain Stimulation"[Mesh] OR Neurofeedback[tw] OR "brain stimulation"[Title/Abstract] OR ((complement*[tw] OR CAM[tiab]) AND therap*[tw]) OR “collaborative care”[ALL FIELDS] OR “coordinated care”[tw] OR “co-located care”[ALL FIELDS] OR “co-managed care”[ALL FIELDS} OR “shared care”[tw] OR “stepped care”[ALL FIELDS] OR REBT[Title/Abstract] OR “Rational Emotive Behavior Therapy”[ALL FIELDS] OR “Mindfulness Based Stress Reduction”[ALL FIELDS] OR MBSR[Title/Abstract] OR “Mindfulness Meditation”[ALL FIELDS] OR Meditation[tw] OR “relaxation therapy”[All Fields] OR Hypnosis[Mesh] OR "Hypnosis, Anesthetic"[Mesh] OR autohypno*[tw] OR auto-hypno*[tw] or hypnosis[tw] OR hypnot*[tw] OR hypnotherap*[tw] OR hypno-therap*[tw] OR posthypnot*[tw] OR post-hypnot*[tw] OR selfhypno*[tw] OR self-hypno*[tw] OR (guided[tw] AND (imagery[tw] OR visualization[tw] OR visualization[tw])) OR (autogenic*[tw] AND train*[tw]) OR (imagery[tw] AND therap*[tw]) OR "integrative restoration"[tw] OR (irest[tw] NOT "international reading speed") or "Katathym-imaginative Psychotherapy"[tw] OR "mental practice"[tw] OR "mental rehearsal"[tw] OR "mind-body"[tw] OR "Biofeedback, Psychology"[Mesh] OR biofeedback*[tw] OR bio-feedback*[tw] or neuro-feedback*[tw] OR Neuro-therap*[tw] OR neurotherap*[tw] OR (autonomic*[tw] AND train*[tw]) OR “Combined Modality Therapy”[ALL FIELDS] OR Diet Therapy[Mesh] OR Exercise[Mesh] OR Exercise[tw] OR “Physical Activity”[ALL FIELDS] OR "Relaxation Therapy"[ALL FIELDS] OR Yoga[tw] OR Acupuncture[tw] OR "Tai Ji"[Mesh] OR "tai chi"[ALL FIELDS] OR “music therapy”[ALL FIELDS] OR “art therapy”[ALL FIELDS] OR “massage therapy”[ALL FIELDS] OR Spirituality[tw] OR “Dietary Supplements”[Mesh:NoExp] OR “St. John’s Wort”[ALL FIELDS] OR Hypericum[tw] OR Inositol[tw] OR Melatonin[tw] OR SAMe[tw] OR Selenium[tw] OR L-tryptophan[tw] OR “Folic Acid”[ALL FIELDS] OR Folate[tw] OR “Fish Oil”[ALL FIELDS] OR “Omega-3 Fatty Acids”[ALL FIELDS] OR 5-HTP[tw] OR “Vitamin E”[ALL FIELDS] OR Zinc[tw] OR Chromium[tw] OR “Gingko biloba”[ALL FIELDS])	2242526
#7	Search (#1 and #6)	61739
#8	Search (#3 or #5 or #7)	158187
#9	Search ((#8 AND Humans[Mesh:NOEXP]) OR (#8 NOT Animals[Mesh:NOEXP])	139249
#10	Search (#8 AND Humans[Mesh:NOEXP]) OR (#8 NOT Animals[Mesh:NOEXP]) Filters: Humans	122798
#11	Search ((#8 AND Humans[Mesh:NOEXP]) OR (#8 NOT Animals[Mesh:NOEXP])) Filters: Humans; Child: birth-18 years	26519

Search	PubMed Query	Items found
#12	Search (Children*[Title/Abstract] OR child[Title/Abstract] OR childhood[Title/Abstract] OR teen[Title/Abstract] OR teens[Title/Abstract] OR teenage*[Title/Abstract] OR pediatric*[Title/Abstract] OR paediatric*[Title/Abstract] OR adolescen*[Title/Abstract] OR boys[Title/Abstract] OR girls[Title/Abstract] OR youth[Title/Abstract] OR youths[Title/Abstract])	1592574
#13	Search (#10 and #12)	14945
#14	Search (#11 or #13)	28875
#15	Search (#11 or #13) Filters: Randomized Controlled Trial	3883
#16	Search (#11 or #13) Filters: Randomized Controlled Trial; Controlled Clinical Trial	4262
#17	Search (#11 or #13) Filters: Randomized Controlled Trial; Controlled Clinical Trial; Clinical Trial	5096
#18	Search ((randomized[title/abstract] AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	716633
#19	Search (#14 and #18)	4787
#20	Search (#17 or #19)	5513
#21	Search ("Case Reports"[pt] OR Editorial[pt] OR Letter[pt] OR News[pt])	3336021
#22	Search (#20 not #21)	**5459**
#23	Search (“systematic review”[ti] OR “meta-analysis”[pt] OR “meta-analysis”[ti] OR “systematic literature review”[ti] OR “this systematic review”[tw] OR (“systematic review”[tiab] AND review[pt]) OR meta synthesis[ti] OR “cochrane database syst rev”[ta])	185192
#24	Search (#14 and #23)	636
#25	Search (#24 not #21)	**631**

Search	PubMed Query	Items found
#26	Search (Harm*[Title/Abstract] OR adverse effects[SH] OR chemically induced[SH] OR drug effects[SH] OR mortality[SH] OR poisoning[SH] OR toxicity[SH] OR adverse effect*[Title/Abstract] OR adverse event*[Title/Abstract] OR adverse reaction*[Title/Abstract] OR Adverse Drug Reaction Reporting Systems[MeSH] OR Accidents[Mesh] OR accident*[Title/Abstract] OR Drug Toxicity[MeSH] OR Drug Hypersensitivity[MeSH] OR Death[MeSH] OR death*[Title/Abstract] OR Suicide[MeSH] OR Suicide, Attempted[MeSH] OR suicide[Title/Abstract] OR suicidal*[Title/Abstract] OR mania[Title/Abstract] OR manic episode*[Title/Abstract] OR overdos*[TW] OR self damage*[Title/Abstract] OR self injur*[Title/Abstract] OR “Self Injurious Behavior”[MeSH] OR self inflict*[Title/Abstract])	5827694
#27	Search (#14 and #26)	8380
#28	Search ("Antidepressive Agents, Second-Generation/adverse effects"[Mesh] OR "Antidepressive Agents, Second-Generation/poisoning"[Mesh] OR "Antidepressive Agents, Second-Generation/toxicity"[Mesh] OR "Serotonin Uptake Inhibitors/adverse effects"[Mesh] OR "Serotonin Uptake Inhibitors/poisoning"[Mesh] OR "Serotonin Uptake Inhibitors/toxicity"[Mesh] OR "Fluoxetine/adverse effects"[Mesh] OR "Fluoxetine/poisoning"[Mesh] OR "Fluoxetine/toxicity"[Mesh] OR "Fluvoxamine /adverse effects"[Mesh] OR "Fluvoxamine /poisoning"[Mesh] OR "Fluvoxamine /toxicity"[Mesh] OR "Paroxetine /adverse effects"[Mesh] OR "Paroxetine /poisoning"[Mesh] OR "Paroxetine /toxicity"[Mesh] OR "Sertraline /adverse effects"[Mesh] OR "Sertraline /poisoning"[Mesh] OR "Sertraline /toxicity"[Mesh] OR "Citalopram /adverse effects"[Mesh] OR "Citalopram /poisoning"[Mesh] OR "Citalopram /toxicity"[Mesh] OR “Trazodone/adverse effects”[Mesh] OR “Trazodone/poisoning”[Mesh] OR “Trazodone/toxicity”[Mesh] OR "Vilazodone Hydrochloride/adverse effects"[Mesh] OR "Vilazodone Hydrochloride/poisoning"[Mesh])	9180
#29	Search (#28 AND Humans[Mesh:NOEXP]) OR (#28 NOT Animals[Mesh:NOEXP])	8784
#30	Search (#28 AND Humans[Mesh:NOEXP]) OR (#28 NOT Animals[Mesh:NOEXP]) Filters: English	7999
#31	Search (#28 AND Humans[Mesh:NOEXP]) OR (#28 NOT Animals[Mesh:NOEXP]) Filters: English; Child: birth-18 years	1754
#32	Search (#30 and #12)	659
#33	Search (#31 or #32)	1833
#34	Search (#33 not #21)	1336
#35	Search (#34 not (#22 or #25))	**932**

Search	PubMed Query	Items found
#36	Search (#23 and #35) (16 of the 932 results are systematic reviews)	**16**

Cochrane Library, 7-25-18

Benefits:

SRs – 183 total

Cochrane Reviews – 103, all imported

80 Other Reviews – 80, all imported

RCTs – 5673, 5475 imported

Harms:

299 total:

Cochrane Reviews – 83, 0 imported

Other Reviews = 7, 5 imported

Trials – 197, 125 imported

Methods Studies – 3, 2 imported

Economic Evaluations – 9, 9 imported

ID	Cochrane Library Search	Hits
#1	[mh "Depressive Disorder"] or [mh "Depressive Disorder, Major"] or [mh Depression] or depress*:ti,ab or depression:ti,ab or depressive:ti,ab or depressed:ti,ab or [mh "Dysthymic Disorder"] or dysthymia:ti,ab,kw or dysthymic:ti,ab,kw or "Persistent Depressive Disorder":ti,ab,kw	56994
#2	[mh "Antidepressive Agents, Second-Generation"] or [mh "Serotonin Uptake Inhibitors"] or [mh "Antidepressive Agents"] or antidepressant*:ti,ab or antidepressives:ti,ab or "antidepressive agent":ti,ab or "antidepressive agents":ti,ab or "antidepressive drug":ti,ab or "antidepressive drugs":ti,ab or "selective serotonin reuptake inhibitor":ti,ab or "selective serotonin reuptake inhibitors":ti,ab or ssri:ti,ab or ssris:ti,ab or [mh Fluoxetine] or fluoxetine:ti,ab or [mh "Vilazodone Hydrochloride"] or vilazodone:ti,ab or Prozac:ti,ab or [mh Fluvoxamine] or Fluvoxamine:ti,ab or mirtazapine:ti,ab,kw or nefazodone:ti,ab,kw or [mh Trazodone] or trazodone:ti,ab or vortioxetine:ti,ab,kw or luvox:ti,ab or [mh Paroxetine] or paroxetine:ti,ab or paxil:ti,ab or [mh Sertraline] or sertraline:ti,ab or Zoloft:ti,ab or [mh Citalopram] or citalopram:ti,ab or celexa:ti,ab or escitalopram:ti,ab,kw or Lexapro:ti,ab or "serotonin norepinephrine reuptake inhibitors":ti,ab,kw or snri*:ti,ab,kw or "norepinephrine reuptake inhibitors":ti,ab,kw or venlafaxine:ti,ab,kw or duloxetine:ti,ab,kw or [mh Bupropion] or Bupropion:ti,ab,kw	21402
#3	#1 and #2	13308

ID	Cochrane Library Search	Hits
#4	[mh Psychotherapy] or [mh "Psychotherapy, Brief"] or [mh "Psychotherapy, Group"] or psychotherapy*:ti,ab or [mh "Cognitive Therapy"] or (cognitive:ti,ab and (therap*:ti,ab or treatment*:ti,ab or intervention*:ti,ab)) or [mh "Behavior Therapy"] or (behavior*:ti,ab and (therap*:ti,ab or treatment*:ti,ab or intervention*:ti,ab)) or CBT:ti,ab or (interpersonal:ti,ab and therap*:ti,ab) or (interpersonal:ti,ab and intervention*:ti,ab) or IPT:ti,ab or e-health:ti,ab or ehealth:ti,ab or (Internet:ti,ab and health*:ti,ab) or "behavioral activation":ti,ab or [mh "Delivery of Health Care, Integrated"] or "integrated care":ti,ab or "integrative care":ti,ab or [mh "Self-Help Groups"] or "self help":ti,ab or [mh "Family Therapy"] or "family support":ti,ab or (parent*:ti,ab and education:ti,ab) or [mh Parents/ED] or [mh Counseling] or [mh "Directive Counseling"] or counsel*:ti,ab or [mh "Problem Solving"] or "problem solving":ti,ab or [mh "Adaptation, Psychological"] or "coping skills":ti,ab or [mh Phototherapy] or "light therapy":ti,ab or phototherapy:ti,ab or "light therapies":ti,ab	95068
#5	#1 and #4	16874

ID	Cochrane Library Search	Hits
#6	[mh "Deep Brain Stimulation"] or Neurofeedback:ti,ab,kw or "brain stimulation":ti,ab,kw or ((complement*:ti,ab or CAM:ti,ab) and therap*:ti,ab,kw) or "collaborative care":ti,ab,kw or "coordinated care":ti,ab,kw or "co-located care":ti,ab,kw or "co-managed care":ti,ab,kw or "shared care":ti,ab,kw or "stepped care":ti,ab,kw or REBT:ti,ab or "Rational Emotive Behavior Therapy":ti,ab,kw or "Mindfulness Based Stress Reduction":ti,ab,kw or MBSR:ti,ab or "Mindfulness Meditation":ti,ab,kw or Meditation:ti,ab,kw or "relaxation therapy":ti,ab,kw or [mh Hypnosis] or [mh "Hypnosis, Anesthetic"] or autohypno*:ti,ab,kw or auto-hypno*:ti,ab,kw or hypnosis:ti,ab,kw or hypnot*:ti,ab,kw or hypnotherap*:ti,ab,kw or hypno-therap*:ti,ab,kw or posthypnot*:ti,ab,kw or post-hypnot*:ti,ab,kw or selfhypno*:ti,ab,kw or self-hypno*:ti,ab,kw or (guided:ti,ab,kw and (imagery:ti,ab,kw or visualization:ti,ab,kw or visualization:ti,ab,kw)) or (autogenic*:ti,ab,kw and train*:ti,ab,kw) or (imagery:ti,ab,kw and therap*:ti,ab,kw) or "integrative restoration":ti,ab,kw or (irest:ti,ab,kw not "international reading speed") or "Katathym-imaginative Psychotherapy":ti,ab,kw or "mental practice":ti,ab,kw or "mental rehearsal":ti,ab,kw or "mind-body":ti,ab,kw or [mh "Biofeedback, Psychology"] or biofeedback*:ti,ab,kw or bio-feedback*:ti,ab,kw or neuro-feedback*:ti,ab,kw or neuro-therap*:ti,ab,kw or neurotherap*:ti,ab,kw or (autonomic*:ti,ab,kw and train*:ti,ab,kw) or "Combined Modality Therapy":ti,ab,kw or [mh "Diet Therapy"] or [mh Exercise] or Exercise:ti,ab,kw or "Physical Activity":ti,ab,kw or "Relaxation Therapy":ti,ab,kw or Yoga:ti,ab,kw or Acupuncture:ti,ab,kw or [mh "Tai Ji"] or "tai chi":ti,ab,kw or "music therapy":ti,ab,kw or "art therapy":ti,ab,kw or "massage therapy":ti,ab,kw or Spirituality:ti,ab,kw or [mh ^"Dietary Supplements"] or "St. John's Wort":ti,ab,kw or Hypericum:ti,ab,kw or Inositol:ti,ab,kw or Melatonin:ti,ab,kw or SAMe:ti,ab,kw or Selenium:ti,ab,kw or L-tryptophan:ti,ab,kw or "Folic Acid":ti,ab,kw or Folate:ti,ab,kw or "Fish Oil":ti,ab,kw or "Omega-3 Fatty Acids":ti,ab,kw or 5-HTP:ti,ab,kw or "Vitamin E":ti,ab,kw or Zinc:ti,ab,kw or Chromium:ti,ab,kw or "Gingko biloba":ti,ab,kw	215436
#7	#1 and #6	13695
#8	#3 or #5 or #7	35170
#9	Children*:ti,ab,kw or child:ti,ab,kw or childhood:ti,ab,kw or teen:ti,ab,kw or teens:ti,ab,kw or teenage*:ti,ab,kw or pediatric*:ti,ab,kw or paediatric*:ti,ab,kw or adolescen*:ti,ab,kw or boys:ti,ab,kw or girls:ti,ab,kw or youth:ti,ab,kw or youths:ti,ab,kw	207538
#10	#8 and #9	5949
#11	(review and systematic) or "systematic review" or ("review literature as topic" and systematic) or "meta-analysis"	65642
#12	#10 and #11 in Cochrane Reviews (Reviews and Protocols) and Other Reviews	**183**

ID	Cochrane Library Search	Hits
#13	((controlled:ti or controlled:ab) and (trial:ti or trial:ab)) or "controlled clinical trial" or "randomized controlled trial":pt or "randomized controlled trial as topic":pt or "single-blind method":pt or "double-blind method":pt or "random allocation":pt	737147
#14	#10 in Trials	5698
#15	"Case Reports":pt or Editorial:pt or Letter:pt or News:pt	10426
#16	#14 not (#15 or #12)	**5673**
#17	Harm*:ti,ab,kw or [mh "Long Term Adverse Effects"] or [mh /AE,CI,DE,MO,PO,TO] or adverse effect*:ti,ab or adverse event*:ti,ab or adverse reaction*:ti,ab or "adverse outcome":ti,ab or "adverse outcomes":ti,ab or [mh "Adverse Drug Reaction Reporting Systems"] or [mh Accidents] or accident*:ti,ab or [mh "Drug Toxicity"] or [mh "Drug Hypersensitivity"] or [mh Death] or death*:ti,ab or [mh Suicide] or [mh "Suicide, Attempted"] or suicide:ti,ab or suicidal*:ti,ab or mania:ti,ab or "manic episode" *:ti,ab or overdos*:ti,ab or self damage*:ti,ab or self injur*:ti,ab or [mh "Self Injurious Behavior"] or self inflict*:ti,ab	367833
#18	#10 and #17	1974
#19	[mh "Antidepressive Agents, Second-Generation"/AE] or [mh "Antidepressive Agents, Second-Generation"/PO] or [mh "Antidepressive Agents, Second-Generation"/TO] or [mh "Serotonin Uptake Inhibitors"/AE] or [mh "Serotonin Uptake Inhibitors"/PO] or [mh "Serotonin Uptake Inhibitors"/TO] or [mh Fluoxetine/AE] or [mh Fluoxetine/PO] or [mh Fluoxetine/TO] or [mh Fluvoxamine/AE] or [mh Fluvoxamine/PO] or [mh Fluvoxamine/TO] or [mh Paroxetine/AE] or [mh Paroxetine/PO] or [mh Paroxetine/TO] or [mh Sertraline/AE] or [mh Sertraline/PO] or [mh Sertraline/TO] or [mh Citalopram/AE] or [mh Citalopram/PO] or [mh Citalopram/TO] or [mh Trazodone/AE] or [mh Trazodone/PO] or [mh Trazodone/TO] or [mh "Vilazodone Hydrochloride"/AE] or [mh "Vilazodone Hydrochloride"/PO]	1552
#20	#19 and #9	429
#21	#18 or #20	2107
#22	#21 not #15	2096
#23	#22 not (#12 or #16)	**299**

PsycInfo, 7-25-18

Benefits:

Clinical Trials = 515, 359 imported

Systematic Reviews = 260, 192 imported

Harms:

Total = 2058, 1975 imported (none were indexed as systematic reviews)

#	Query	Limiters/Expanders	Results
S1	DE "Depression (Emotion)") OR (DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR depressive OR depression OR depressed OR dysthymic OR dysthymia	Search modes - Boolean/Phrase	331,438
S2	TX “antidepress* OR TX Bupropion OR TX Celexa OR TX Citalopram OR TX Duloxetine OR TX Escitalopram OR TX Fluoxetine OR TX Fluvoxamine OR TX Lexapro OR TX Luvox OR TX Mirtazapine OR TX Nefazodone OR TX Paroxetine OR TX Paxil OR TX Prozac OR TX Sertraline OR TX Trazodone OR TX Venlafaxine OR TX Vilazodone OR TX Vortioxetine OR TX Zoloft OR TX “norepinephrine reuptake inhibitor” OR TX “norepinephrine reuptake inhibitors” TX “selective serotonin reuptake inhibitor” OR TX “selective serotonin reuptake inhibitors” OR TX “serotonin uptake inhibitor” OR TX “serotonin uptake inhibitors” OR TX SSRI OR TX SSRIs OR TX "serotonin norepinephrine reuptake inhibitor" TX "serotonin norepinephrine reuptake inhibitors" OR TX SNRI OR TX SNRIs	Search modes - Boolean/Phrase	685
S3	S1 AND S2	Search modes - Boolean/Phrase	478

#	Query	Limiters/Expanders	Results
S4	DE "Psychotherapy" OR DE "Adolescent Psychotherapy" OR DE "Affirmative Therapy" OR DE "Analytical Psychotherapy" OR DE "Autogenic Training" OR DE "Behavior Therapy" OR DE "Brief Psychotherapy" OR DE "Brief Relational Therapy" OR DE "Child Psychotherapy" OR DE "Client Centered Therapy" OR DE "Cognitive Behavior Therapy" OR DE "Conversion Therapy" OR DE "Eclectic Psychotherapy" OR DE "Emotion Focused Therapy" OR DE "Existential Therapy" OR DE "Experiential Psychotherapy" OR DE "Expressive Psychotherapy" OR DE "Eye Movement Desensitization Therapy" OR DE "Feminist Therapy" OR DE "Gestalt Therapy" OR DE "Group Psychotherapy" OR DE "Guided Imagery" OR DE "Humanistic Psychotherapy" OR DE "Hypnotherapy" OR DE "Individual Psychotherapy" OR DE "Insight Therapy" OR DE "Integrative Psychotherapy" OR DE "Interpersonal Psychotherapy" OR DE "Logotherapy" OR DE "Narrative Therapy" OR DE "Network Therapy" OR DE "Persuasion Therapy" OR DE "Primal Therapy" OR DE "Psychoanalysis" OR DE "Psychodrama" OR DE "Psychodynamic Psychotherapy" OR DE "Psychotherapeutic Counseling" OR DE "Rational Emotive Behavior Therapy" OR DE "Reality Therapy" OR DE "Relationship Therapy" OR DE "Solution Focused Therapy" OR DE "Supportive Psychotherapy" OR DE "Transactional Analysis"	Search modes - Boolean/Phrase	202,006
S5	DE "Behavioral Activation System" OR DE "Integrated Services" OR DE "Family Therapy" OR DE "Conjoint Therapy" OR DE "Strategic Family Therapy" OR DE "Structural Family Therapy" OR DE "Self-Help Techniques" OR DE "Self-Management" OR DE "Counseling" OR DE "Community Counseling" OR DE "Cross Cultural Counseling" OR DE "Educational Counseling" OR DE "Group Counseling" OR DE "Microcounseling" OR DE "Multicultural Counseling" OR DE "Occupational Guidance" OR DE "Pastoral Counseling" OR DE "Peer Counseling" OR DE "Premarital Counseling" OR DE "Psychotherapeutic Counseling" OR DE "Rehabilitation Counseling" OR DE "School Counseling"	Search modes - Boolean/Phrase	90,266

#	Query	Limiters/Expanders	Results
S6	TX “cognitive behavior therapy” OR TX CBT OR TX “cognitive therapy” OR TX psychotherapy OR (cognitive AND (therap* OR treatment* OR intervention*)) OR (behavior* AND (therap* OR treatment* OR intervention*)) OR (interpersonal AND (therap* OR psychotherapy*)) OR TX IPT OR TX e-health OR TX ehealth OR (Internet* AND Health*) OR TX “behavioral activation” OR TX “delivery of health care” OR (integrat* AND (service* OR care*)) OR TX “family support” OR (Parent* and education*) OR TX counsel* OR TX "Problem Solving"	Search modes - Boolean/Phrase	977,193
S7	DE "Emotional Adjustment" OR DE "Emotional Control" OR DE "Identity Crisis" OR TX “psychological adaptation” OR DE "Coping Behavior" OR TX “coping skills” OR TX Phototherapy OR TX “light therapy” OR TX “Deep Brain Stimulation”	Search modes - Boolean/Phrase	72,244

#	Query	Limiters/Expanders	Results
S8	TX "Alternative Medicine" OR TX Acupuncture OR TX Aromatherapy OR TX Folk Medicine OR TX Faith Healing OR TX CAM OR (complement* AND therap*) OR TX “collaborative care” OR TX “coordinated care” OR TX “co-located care” OR TX “co-managed care” OR TX “shared care” OR TX “stepped care” OR TX "Rational Emotive Behavior Therapy" OR TX “Mindfulness Based Stress Reduction” OR TX MBSR OR TX “Mindfulness Meditation” OR TX Meditation OR TX “relaxation therapy” OR TX Hypnosis OR TX autohypno* OR TX auto-hypno* or TX hypnosis OR TX hypnot* OR TX hypnotherap* OR TX hypno-therap* OR TX posthypnot* OR TX post-hypnot* OR TX selfhypno* OR TX self-hypno* OR (TX guided AND (TX imagery OR TX visualization OR TX visualization)) OR (TX autogenic* AND train*) OR (TX imagery AND TX therap*) OR TX "integrative restoration" OR (TX irest NOT "international reading speed") or TX "Katathym-imaginative Psychotherapy" OR TX "mental practice" OR TX "mental rehearsal" OR TX "mind-body" OR TX biofeedback* OR TX bio-feedback* or TX Neurofeedback OR TX neuro-feedback* OR TX neuro-therap* OR TX neurotherap* OR (TX autonomic* AND TX train*) OR TX “Combined Modality Therapy” OR DE "Dietary Restraint" OR TX “diet therapy” OR TX "Dietary Supplements" OR DE "Exercise" OR DE "Aerobic Exercise" OR TX "Weightlifting" OR TX "Yoga" OR TX "Physical Activity" OR TX "Relaxation Therapy" OR TX "Progressive Relaxation Therapy" OR TX “tai ji” OR TX “tai chi” OR TX "Music Therapy" OR TX "Art Therapy" OR TX “Massage Therapy” OR TX Spirituality OR DE "Dietary Supplements" OR DE "Hypericum Perforatum" OR TX “St. John’s Wort” OR TX Hypericum OR TX Inositol OR TX Melatonin OR TX SAMe OR TX Selenium OR TX “L-tryptophan” OR TX “Folic Acid” OR TX Folate OR TX “Fish Oil” OR TX Omega-3 Fatty Acids” OR TX 5-HTP OR TX “Vitamin E” OR TX Zinc OR TX Chromium OR TX "Gingko biloba"	Search modes - Boolean/Phrase	439,277
S9	S4 OR S5 OR S6 OR S7 OR S8	Search modes - Boolean/Phrase	1,382,239

#	Query	Limiters/Expanders	Results
S10	S1 AND S9	Search modes - Boolean/Phrase	141,182
S11	S3 OR S10	Search modes - Boolean/Phrase	141,461
S12	S11	Limiters - English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human; Methodology: CLINICAL TRIAL Search modes - Boolean/Phrase	**515**
S13	S11	Limiters - English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human; Methodology: - Systematic Review, META ANALYSIS, METASYNTHESIS Search modes - Boolean/Phrase	261
S14	S13 NOT S12	Search modes - Boolean/Phrase	**260**

#	Query	Limiters/Expanders	Results
S15	MM "Accidents" OR TX “Adverse Effects" OR TX “adverse effect” or TX “adverse event” OR TX “adverse events” OR TX "adverse outcome" OR TX "adverse outcomes" OR TX “adverse reaction” OR TX “adverse reactions” OR TX “chemically induced” OR MM "Death and Dying" OR DE "Drug Allergies" OR DE "Drug Dependency" OR TX “drug effects” OR DE "Drug Sensitivity" OR TX harm* OR TX "manic episode" OR TX mortality OR TX overdose OR DE "Patient Safety" OR TX “self damage” OR DE "Self-Injurious Behavior" OR DE "Side Effects (Drug)" OR MM "Suicide" OR MM "Toxicity" OR MM "Neurotoxicity"	Search modes - Boolean/Phrase	209,173
S16	S11 and S15	Search modes - Boolean/Phrase	13,380
S17	S16	Limiters - English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Search modes - Boolean/Phrase	2,176
S18	S17 and (S12 or S14)	Limiters - English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Search modes - Boolean/Phrase	118

#	Query	Limiters/Expanders	Results
S19	S17 not S18	Limiters - English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Search modes - Boolean/Phrase	**2,058**
S20	S19	Limiters - Methodology: - Systematic Review, META ANALYSIS, METASYNTHESIS Search modes - Boolean/Phrase	0

Cumulative Index to Nursing and Allied Health (CINAHL), 7-27-18

All results limited to Non-Medline

Clinical Trials = 297, 261 imported

Systematic Reviews / Meta-analyses = 145, 145 imported

Harms:

systematic review/meta-analyses = 10, 5 imported

Other study designs = 279, 263 imported, 253 remain

(*10 were letters, comments, or editorials and were removed manually from ENDNOTE after import, as the NOT feature in CINAHL stopped working)

(*Sent separate EndNote library for CINAHL results to incorporate to the PubMed, PsycInfo and Cochrane Library results.)

#	CINAHL Query	Limiters/Expanders	Results
1	MH Depression+ OR TI depress* OR AB depress* OR TI depression OR AB depression OR TI depressive OR AB depressive OR TI depressed OR AB depressed OR dysthymia OR dysthymic	Search modes - Boolean/Phrase	134,004

#	CINAHL Query	Limiters/Expanders	Results
2	MH "Antidepressive Agents+" OR MH "Serotonin Uptake Inhibitors+" OR TI antidepressant* OR AB antidepressant* OR TI antidepressives OR "antidepressive agent" OR "antidepressive agents" OR "antidepressive drug" OR "antidepressive drugs" OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR ssri OR ssris OR Fluoxetine OR vilazodone OR Prozac OR Fluvoxamine OR "mirtazapine" OR "nefazodone" OR trazodone OR "vortioxetine" OR luvox OR Paroxetine OR paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR "serotonin norepinephrine reuptake inhibitors" OR snri* OR "norepinephrine reuptake inhibitors" OR venlafaxine OR duloxetine OR Bupropion	Search modes - Boolean/Phrase	28,637
3	S1 AND S2	Search modes - Boolean/Phrase	14,029
4	Psychotherapy OR "Cognitive Therapy" OR (cognitive AND (therap* OR treatment* OR intervention*)) OR "Behavior Therapy" OR (behavior* AND (therap* OR treatment* OR intervention*)) OR CBT OR (interpersonal AND therap*) OR (interpersonal AND intervention*) OR IPT OR e-health OR ehealth OR (Internet AND health) OR "behavioral activation" OR "Integrated Delivery of Health Care" OR "integrated care" OR "integrative care" OR "self help" OR Family Therapy OR "family support" OR (parent* AND education) OR counsel* OR "Problem Solving" OR "Psychological adaptation" OR "coping skills" OR "light therapy" OR phototherapy OR "light therapies"	Search modes - Boolean/Phrase	290,273
5	S1 AND S4	Search modes - Boolean/Phrase	27,430

#	CINAHL Query	Limiters/Expanders	Results
6	"Deep Brain Stimulation" OR Neurofeedback OR "brain stimulation" OR ((complement* OR CAM) AND therap*) OR “collaborative care” OR “coordinated care” OR “co-located care” OR “co-managed care” OR “shared care” OR “stepped care” OR REBT OR “Rational Emotive Behavior Therapy” OR “Mindfulness Based Stress Reduction” OR MBSR OR Meditation OR “relaxation therapy” OR Hypnosis OR autohypno* OR auto-hypno* OR hypnot* OR hypnotherap* OR hypno-therap* OR posthypnot* OR post-hypnot* OR selfhypno* OR self-hypno* OR (guided AND (imagery OR visualization) OR (autogenic* AND train*) OR (imagery AND therap*) OR "integrative restoration" OR (irest NOT "international reading speed") or "Katathym-imaginative Psychotherapy" OR "mental practice" OR "mental rehearsal" OR "mind-body" OR "Biofeedback, Psychology" OR biofeedback* OR bio-feedback* or neuro-feedback* OR Neuro-therap* OR neurotherap* OR (autonomic* AND train*) OR “Combined Modality Therapy” OR “Diet Therapy” OR Exercise OR “Physical Activity” OR "Relaxation Therapy" OR Yoga OR Acupuncture OR "Tai Ji" OR "tai chi" OR “music therapy” OR “art therapy” OR “massage therapy” OR Spirituality OR “Dietary Supplements” OR “dietary supplement” OR “St. John’s Wort” OR Hypericum OR Inositol OR Melatonin OR SAMe OR Selenium OR L-tryptophan OR “Folic Acid” OR Folate OR “Fish Oil” OR “Omega-3 Fatty Acids” OR 5-HTP OR “Vitamin E” OR Zinc OR Chromium OR “Gingko biloba”	Search modes - Boolean/Phrase	442,461
7	S1 and S6	Search modes - Boolean/Phrase	18,525
8	S3 or S5 or S7	Search modes - Boolean/Phrase	49,848
9	S8	Limiters - English Language; Human; Age Groups: Adolescent: 13-18 years, All Child Search modes - Boolean/Phrase	6,786

#	CINAHL Query	Limiters/Expanders	Results
10	(Children* OR child OR childhood OR teen OR teens OR teenage* OR pediatric* OR paediatric* OR adolescen* OR boys OR girls OR youth OR youths)	Search modes - Boolean/Phrase	886,762
11	S8	Limiters - English Language; Human Search modes - Boolean/Phrase	28,398
12	S10 AND S11	Search modes - Boolean/Phrase	7,582
13	S9 OR S12	Search modes - Boolean/Phrase	7,720
14	S13	Limiters - Publication Type: Clinical Trial, Randomized Controlled Trial Search modes - Boolean/Phrase	1,320
15	((randomized AND controlled AND trial) OR (controlled AND trial) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method" OR "Double-Blind Method" OR "Random Allocation")	Search modes - Boolean/Phrase	147,471
16	S13 and S15	Search modes - Boolean/Phrase	1,163
17	S14 OR S16	Search modes - Boolean/Phrase	1,599
18	S17	Limiters - Publication Type: Case Study, Editorial, Letter Search modes - Boolean/Phrase	20
19	S17 NOT S18	Search modes - Boolean/Phrase	1,579
20	S19	Limiters - Exclude MEDLINE records Search modes - Boolean/Phrase	297

#	CINAHL Query	Limiters/Expanders	Results
21	S13	Limiters - Publication Type: Meta Analysis, Meta Synthesis, Systematic Review Search modes - Boolean/Phrase	365
22	S21	Limiters - Exclude MEDLINE records Search modes - Boolean/Phrase	145
23	Harm* OR MW “adverse effects” OR MW “chemically induced” OR MW “drug effects” OR MW mortality OR MW poisoning OR MW toxicity OR adverse effect* OR adverse event* OR adverse reaction* OR “Adverse Drug Reaction Reporting Systems” OR Accidents OR accident* OR “Drug Toxicity” OR “Drug Hypersensitivity” OR Death OR death* OR Suicide OR suicide OR suicidal* OR mania OR manic episode* OR overdos* OR self damage* OR self injur* OR “Self Injurious Behavior” OR self inflict*	Search modes - Boolean/Phrase	845,535
24	S13 and S23	Search modes - Boolean/Phrase	1,767
25	S24 NOT S19	Search modes - Boolean/Phrase	1,319
26	S25 NOT S21	Search modes - Boolean/Phrase	1,247

#	CINAHL Query	Limiters/Expanders	Results
27	(MH “Antidepressive Agents, Second-Generation” AND “adverse effects”) OR (MH "Antidepressive Agents, Second-Generation” AND poisoning) OR (MH "Antidepressive Agents, Second-Generation” AND toxicity) OR (MH "Serotonin Uptake Inhibitors” AND ”adverse effects") OR (MH "Serotonin Uptake Inhibitors” AND poisoning) OR (MH "Serotonin Uptake Inhibitors” AND toxicity) OR (MH Fluoxetine AND ”adverse effects”) OR (MH Fluoxetine AND poisoning) OR (MH Fluoxetine AND toxicity) OR (MH Fluvoxamine AND “adverse effects") OR (MH Fluvoxamine AND poisoning) OR (MH Fluvoxamine AND toxicity) OR (MH Paroxetine AND “adverse effects") OR (MH Paroxetine AND poisoning) OR (MH Paroxetine AND toxicity) OR (MH Sertraline AND “adverse effects") OR (MH Sertraline AND poisoning) OR (MH Sertraline AND toxicity) OR (MH Citalopram AND “adverse effects") OR (MH Citalopram AND poisoning) OR (MH Citalopram AND toxicity) OR (MH Trazodone AND “adverse effects”) OR (MH Trazodone AND poisoning) OR (MH Trazodone AND toxicity) OR (MH “Vilazodone Hydrochloride” AND “adverse effects") OR (MH "Vilazodone Hydrochloride” AND poisoning)	Search modes - Boolean/Phrase	3,490
28	S27	Limiters - English Language; Human; Age Groups: Adolescent: 13-18 years, All Child Search modes - Boolean/Phrase	256
29	S26 OR S28	Limiters - English Language; Human; Age Groups: Adolescent: 13-18 years, All Child Search modes - Boolean/Phrase	1,285
30	S29	Limiters - Exclude MEDLINE records Search modes - Boolean/Phrase	279

#	CINAHL Query	Limiters/Expanders	Results
31	S30	Limiters - Publication Type: Meta Analysis, Meta Synthesis, Systematic Review Search modes - Boolean/Phrase	10
32	S30	Limiters - Publication Type: Case Study, Editorial, Letter Search modes - Boolean/Phrase **REMOVED MANUALLY**	10

Addendum 2 ("A2") Targeted extra searches for specific older, rarely used drugs (tricyclics and MAO Inhibitors) August 6-7, 2018

Searches run and imported to previous results, removing duplicates = **832** citations total in A2 EndNote library, 'A2 Childhood Depression Older Drugs.enl'.

First three indexes searched 8/6 and CINAHL searched 8/7.

There were no new results for CINAHL, so all A2 results are effectively from 8/6/18.

PubMed:

Trials = 613, 183 imported

SRs = 34, 2 imported

HARMS:

SRs = 9, 8 imported

Other study designs = 483, 441 imported

Search	Query	Items found
#1	Search "Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH] OR Depression[MeSH] OR depress*[Title/Abstract] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed[Title/Abstract] OR "Dysthymic Disorder"[Mesh] OR dysthymia OR dysthymic OR "Persistent Depressive Disorder"[ALL FIELDS]	450963

Search	Query	Items found
#2	Search ("Amitriptyline"[Mesh] OR Amitriptyline[tiab] OR "Desipramine"[Mesh] OR desipramine[tiab] OR "Imipramine"[Mesh] OR imipramine[tiab] OR "Nortriptyline"[Mesh] OR nortriptyline[tiab] OR "Doxepin"[Mesh] OR doxepin[tiab] OR "Clomipramine"[Mesh] OR clomipramine[tiab] OR Elavil[tiab] OR Enovil[tiab] OR Levate[tiab] OR Anafranail[tiab] OR Norpramin[tiab] OR Pertofrane[tiab] OR Adapin[tiab] OR Silenor[tiab] OR Sinequan[tiab] OR Tofranil[tiab] OR "Aventyl Hydrochloride"[tiab] OR Pamelor[tiab])	30666
#3	Search (#1 and #2)	10192
#4	Search ("Selegiline"[Mesh] or selegiline[tiab] OR Eldepryl[tiab] OR Zelapar[tiab] OR "rasagiline" [Supplementary Concept] OR rasagiline[tiab] OR Azilect[tiab] OR "Isocarboxazid"[Mesh] OR Isocarboxazid[tiab] OR Marplan[tiab] OR "Phenelzine"[Mesh] OR Phenelzine[tiab] OR Nardil[tiab] OR "Tranylcypromine"[Mesh] OR Tranylcypromine[tiab] OR Parnate[tiab] OR Asagiline[tiab])	7008
#5	Search (#1 and #4)	1398
#6	Search (#3 or #5)	11203
#7	Search ((#6 AND Humans[Mesh:NOEXP]) OR (#6 NOT Animals[Mesh:NOEXP]))	9075
#8	Search ((#6 AND Humans[Mesh:NOEXP]) OR (#6 NOT Animals[Mesh:NOEXP])) Filters: Child: birth-18 years	1219
#9	Search ((Children*[Title/Abstract] OR child[Title/Abstract] OR childhood[Title/Abstract] OR teen[Title/Abstract] OR teens[Title/Abstract] OR teenage*[Title/Abstract] OR pediatric*[Title/Abstract] OR paediatric*[Title/Abstract] OR adolescen*[Title/Abstract] OR boys[Title/Abstract] OR girls[Title/Abstract] OR youth[Title/Abstract] OR youths[Title/Abstract]))	1595222
#10	Search (#7 and #9)	313
#11	Search (#8 or #10)	1278
#12	Search (#8 or #10) Filters: Randomized Controlled Trial	341
#13	Search (#8 or #10) Filters: Randomized Controlled Trial; Controlled Clinical Trial	478
#14	Search (#8 or #10) Filters: Randomized Controlled Trial; Controlled Clinical Trial; Clinical Trial	573

Search	Query	Items found
#15	Search ((randomized[title/abstract] AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	717733
#16	Search (#11 and #15)	563
#17	Search (#14 or #16)	621
#18	Search ("Case Reports"[pt] OR Editorial[pt] OR Letter[pt] OR News[pt])	3340307
#19	Search (#17 not #18)	613
#20	Search (“systematic review”[ti] OR “meta-analysis”[pt] OR “meta-analysis”[ti] OR “systematic literature review”[ti] OR “this systematic review”[tw] OR (“systematic review”[tiab] AND review[pt]) OR meta synthesis[ti] OR “cochrane database syst rev”[ta])	186009
#21	Search (#11 and #20)	34
#22	Search ((Harm*[Title/Abstract] OR adverse effects[SH] OR chemically induced[SH] OR drug effects[SH] OR mortality[SH] OR poisoning[SH] OR toxicity[SH] OR adverse effect*[Title/Abstract] OR adverse event*[Title/Abstract] OR adverse reaction*[Title/Abstract] OR Adverse Drug Reaction Reporting Systems[MeSH] OR Accidents[Mesh] OR accident*[Title/Abstract] OR Drug Toxicity[MeSH] OR Drug Hypersensitivity[MeSH] OR Death[MeSH] OR death*[Title/Abstract] OR Suicide[MeSH] OR Suicide, Attempted[MeSH] OR suicide[Title/Abstract] OR suicidal*[Title/Abstract] OR mania[Title/Abstract] OR manic episode*[Title/Abstract] OR overdos*[TW] OR self damage*[Title/Abstract] OR self injur*[Title/Abstract] OR “Self Injurious Behavior”[MeSH] OR self inflict*[Title/Abstract]))	5835890
#23	Search (#11 and #22)	630

Search	Query	Items found
#24	Search ("Amitriptyline/adverse effects"[Mesh] OR "Amitriptyline/poisoning"[Mesh] OR "Amitriptyline/toxicity"[Mesh OR "Desipramine/adverse effects"[Mesh] OR "Desipramine/poisoning"[Mesh] OR "Desipramine/toxicity"[Mesh] OR "Imipramine/adverse effects"[Mesh] OR "Imipramine/poisoning"[Mesh] OR "Imipramine/toxicity"[Mesh] OR "Nortriptyline/adverse effects"[Mesh] OR "Nortriptyline/poisoning"[Mesh] OR "Nortriptyline/toxicity"[Mesh] OR "Doxepin/adverse effects"[Mesh] OR "Doxepin/poisoning"[Mesh] OR "Doxepin/toxicity"[Mesh] OR "Clomipramine/adverse effects"[Mesh] OR "Clomipramine/poisoning"[Mesh] OR "Clomipramine/toxicity"[Mesh] OR "Selegiline/adverse effects"[Mesh] OR "Selegiline/poisoning"[Mesh] OR "Selegiline/toxicity"[Mesh] OR "Isocarboxazid/adverse effects"[Mesh] OR "Isocarboxazid/poisoning"[Mesh] OR "Isocarboxazid/toxicity"[Mesh] OR "Phenelzine/adverse effects"[Mesh] OR "Phenelzine/poisoning"[Mesh] OR "Phenelzine/toxicity"[Mesh] OR "Tranylcypromine/adverse effects"[Mesh] OR "Tranylcypromine/poisoning"[Mesh] OR "Tranylcypromine/toxicity"[Mesh])	3131
#25	Search (#24 AND Humans[Mesh:NOEXP]) OR (#24 NOT Animals[Mesh:NOEXP])	2851
#26	Search (#24 AND Humans[Mesh:NOEXP]) OR (#24 NOT Animals[Mesh:NOEXP]) Sort by: Author Filters: English	2488
#27	Search (#24 AND Humans[Mesh:NOEXP]) OR (#24 NOT Animals[Mesh:NOEXP]) Sort by: Author Filters: English; Child: birth-18 years	493
#28	Search (#26 and #9)	148
#29	Search (#27 or #28)	504
#30	Search (#29 not #18)	377
#31	Search (#30 or #23)	828
#32	Search (#31 NOT (#19 or #21))	492
#33	Search (#31 NOT (#19 or #21)) Sort by: Author Filters: Meta-Analysis	2
#34	Search (#31 NOT (#19 or #21)) Sort by: Author Filters: Meta-Analysis; Systematic Reviews	**9**
#35	Search (#32 not #34)	**483**

Cochrane Library – August 6, 2018

Benefits:

SRs – 10 total
Cochrane Reviews – 9, 0 imported
Other Reviews – 1, 0 imported

Trials – 545, 167 imported

Harms:

8 total:
Cochrane Reviews – 7, 0 imported
Economic Evaluations – 1, 0 imported

ID	Search	Hits
#1	[mh "Depressive Disorder"] or [mh "Depressive Disorder, Major"] or [mh Depression] or depress*:ti,ab or depression:ti,ab or depressive:ti,ab or depressed:ti,ab or [mh "Dysthymic Disorder"] or dysthymia:ti,ab,kw or dysthymic:ti,ab,kw or "Persistent Depressive Disorder":ti,ab,kw	58920
#2	[mh Amitriptyline] or Amitriptyline:ti,ab or [mh Desipramine] or desipramine:ti,ab or [mh Imipramine] or imipramine:ti,ab or [mh Nortriptyline] or nortriptyline:ti,ab or [mh Doxepin] or doxepin:ti,ab or [mh Clomipramine] or clomipramine:ti,ab or Elavil:ti,ab or Enovil:ti,ab or Levate:ti,ab or Anafranail:ti,ab or Norpramin:ti,ab or Pertofrane:ti,ab or Adapin:ti,ab or Silenor:ti,ab or Sinequan:ti,ab or Tofranil:ti,ab or "Aventyl Hydrochloride":ti,ab or Pamelor:ti,ab or [mh Selegiline] or selegiline:ti,ab or Eldepryl:ti,ab or Zelapar:ti,ab or rasagiline:ti,ab,kw or Azilect:ti,ab or [mh Isocarboxazid] or Isocarboxazid:ti,ab or Marplan:ti,ab or [mh Phenelzine] or Phenelzine:ti,ab or Nardil:ti,ab or [mh Tranylcypromine] or Tranylcypromine:ti,ab or Parnate:ti,ab or [mh Asagiline]	6774
#3	#1 and #2	3703
#4	Children*:ti,ab,kw or child:ti,ab,kw or childhood:ti,ab,kw or teen:ti,ab,kw or teens:ti,ab,kw or teenage*:ti,ab,kw or pediatric*:ti,ab,kw or paediatric*:ti,ab,kw or adolescen*:ti,ab,kw or boys:ti,ab,kw or girls:ti,ab,kw or youth:ti,ab,kw or youths:ti,ab,kw	209584
#5	#3 and #4	561
#6	(review and systematic) or "systematic review" or ("review literature as topic" and systematic) or "meta-analysis"	66225
#7	#5 and #6 in Cochrane Reviews (Reviews and Protocols) and Other Reviews	**10**
#8	#5 in Trials	548
#9	"Case Reports":pt or Editorial:pt or Letter:pt or News:pt	10472
#10	#8 not (#9 or #7)	**545**
#11	Harm*:ti,ab,kw or [mh "Long Term Adverse Effects"] or [mh /AE,CI,DE,MO,PO,TO] or adverse effect*:ti,ab or adverse event*:ti,ab or adverse reaction*:ti,ab or "adverse outcome":ti,ab or "adverse outcomes":ti,ab or [mh "Adverse Drug Reaction Reporting Systems"] or [mh Accidents] or accident*:ti,ab or [mh "Drug Toxicity"] or [mh "Drug Hypersensitivity"] or [mh Death] or death*:ti,ab or [mh Suicide] or [mh "Suicide, Attempted"] or suicide:ti,ab or suicidal*:ti,ab or mania:ti,ab or "manic episode" *:ti,ab or overdos*:ti,ab or self damage*:ti,ab or self injur*:ti,ab or [mh "Self Injurious Behavior"] or self inflict*:ti,ab	375282
#12	#5 and #11	295

ID	Search	Hits
#13	[mh Amitriptyline/AE] or [mh Amitriptyline/PO] or [mh Amitriptyline/TO] or [mh Desipramine/AE] or [mh Desipramine/PO] or [mh Desipramine/TO] or [mh Imipramine/AE] or [mh Imipramine/PO] or [mh Imipramine/TO] or [mh Nortriptyline/AE] or [mh Nortriptyline/PO] or [mh Nortriptyline/TO] or [mh Doxepin/AE] or [mh Doxepin/PO] or [mh Doxepin/TO] or [mh Clomipramine/AE] or [mh Clomipramine/PO] or [mh Clomipramine/TO] or [mh Selegiline/AE] or [mh Selegiline/PO] or [mh Selegiline/TO] or [mh Isocarboxazid/AE] or [mh Isocarboxazid/PO] or [mh Isocarboxazid/TO] or [mh Phenelzine/AE] or [mh Phenelzine/PO] or [mh Phenelzine/TO] or [mh Tranylcypromine/AE] or [mh Tranylcypromine/PO] or [mh Tranylcypromine/TO]	1073
#14	#13 and #1 and #4	185
#15	#12 or #14	295
#16	#15 not #9	294
#17	#16 not (#7 or #8)	**8**

PsychInfo, 8/6/18
Clinical Trials = 21, 11 imported
SRs = 3, 0 imported
Harms:
SRs = 0
All other study designs = 61, 20 imported

#	Query	Limiters/Expanders	Results
S1	DE "Depression (Emotion)" OR DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR depressive OR depression OR depressed OR dysthymic OR dysthymia	Search modes - Boolean/Phrase	332,010
S2	TX Amitriptyline or TX Desipramine or TX Imipramine or TX Nortriptyline or TX Doxepin or TX Clomipramine or TX Elavil or TX Enovil or TX Levate or TX Anafranail or TX Norpramin or TX Pertofrane or TX Adapin or TX Silenor or TX Sinequan or TX Tofranil or TX "Aventyl Hydrochloride" or TX Pamelor or TX Selegiline or TX Eldepryl or TX Zelapar or TX rasagiline or TX Azilect or TX Isocarboxazid or TX Marplan or TX Phenelzine or TX Nardil or TX Tranylcypromine or TX Parnate or TX Asagiline	Search modes - Boolean/Phrase	12,870

#	Query	Limiters/Expanders	Results
S3	S1 AND S2	Search modes - Boolean/Phrase	7,227
S4	S3	Limiters - English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Search modes - Boolean/Phrase	291
S5	S4	Limiters - Methodology: CLINICAL TRIAL Search modes - Boolean/Phrase	21
S6	S4	Limiters - Methodology: - Systematic Review, META ANALYSIS, METASYNTHESIS Search modes - Boolean/Phrase	3
S7	MM "Accidents" OR TX “Adverse Effects" OR TX “adverse effect” or TX “adverse event” OR TX “adverse events” OR TX "adverse outcome" OR TX "adverse outcomes" OR TX “adverse reaction” OR TX “adverse reactions” OR TX “chemically induced” OR MM "Death and Dying" OR DE "Drug Allergies" OR DE "Drug Dependency" OR TX “drug effects” OR DE "Drug Sensitivity" OR TX harm* OR TX "manic episode" OR TX mortality OR TX overdose OR DE "Patient Safety" OR TX “self damage” OR DE "Self-Injurious Behavior" OR DE "Side Effects (Drug)" OR MM "Suicide" OR MM "Toxicity" OR MM "Neurotoxicity"	Search modes - Boolean/Phrase	209,568
S8	S4 and S7	Search modes - Boolean/Phrase	70
S9	S8 and (S5 or S6)	Search modes - Boolean/Phrase	9
S10	S8 NOT S9	Search modes - Boolean/Phrase	61
S11	S10	Limiters - Methodology: - Systematic Review, META ANALYSIS, METASYNTHESIS Search modes - Boolean/Phrase	0

CINAHL, 8-7-18
Trials = 15, after excluding Medline, **0**
Systematic Reviews = 11, after excluding Medline, 1 saved, after import to EndNote**, 0**
Harms:

Systematic Reviews = **0**
Other study designs = 3, after excluding Medline, 3 saved, after import to Endnote, **0**

#	Query	Limiters/Expanders	Results
1	MH Depression+ OR TI depress* OR AB depress* OR TI depression OR AB depression OR TI depressive OR AB depressive OR TI depressed OR AB depressed OR dysthymia OR dysthymic	Search modes - Boolean/Phrase	134,366
2	Amitriptyline or Desipramine or Imipramine or Nortriptyline or Doxepin or Clomipramine or Elavil or Enovil or Levate or Anafranail or Norpramin or Pertofrane or Adapin or Silenor or Sinequan or Tofranil or "Aventyl Hydrochloride" or Pamelor or Selegiline or Eldepryl or Zelapar or rasagiline or Azilect or Isocarboxazid or Marplan or Phenelzine or Nardil or Tranylcypromine or Parnate or Asagiline	Search modes - Boolean/Phrase	2,646
3	S1 and S2	Search modes - Boolean/Phrase	726
4	S3	Limiters - Human; Age Groups: Adolescent: 13-18 years, All Child; Language: English Search modes - Boolean/Phrase	37
5	Children* OR child OR childhood OR teen OR teens OR teenage* OR pediatric* OR paediatric* OR adolescen* OR boys OR girls OR youth OR youths	Search modes - Boolean/Phrase	888,755
6	S3	Limiters - Human; Language: English Search modes - Boolean/Phrase	286
7	S5 and S6	Search modes - Boolean/Phrase	45
8	S4 or S7	Search modes - Boolean/Phrase	45

#	Query	Limiters/Expanders	Results
9	S4 or S7	Limiters - Publication Type: Clinical Trial, Randomized Controlled Trial Search modes - Boolean/Phrase	15
10	((randomized AND controlled AND trial) OR (controlled AND trial) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method" OR "Double-Blind Method" OR "Random Allocation")	Limiters - Publication Type: Clinical Trial, Randomized Controlled Trial Search modes - Boolean/Phrase	84,233
11	S8 AND S10	Search modes - Boolean/Phrase	5
12	S9 OR S11	Search modes - Boolean/Phrase	15
13	S12	Limiters - Publication Type: Case Study, Editorial, Letter Search modes - Boolean/Phrase	0
14	S12	Limiters - Publication Type: Case Study, Editorial, Letter Search modes - Boolean/Phrase	0
15	S13	Limiters - Exclude MEDLINE records Search modes - Boolean/Phrase	0
16	S8	Limiters - Publication Type: Meta Analysis, Meta Synthesis, Systematic Review Search modes - Boolean/Phrase	11
17	S16	Limiters - Exclude MEDLINE records Search modes - Boolean/Phrase	1

#	Query	Limiters/Expanders	Results
18	"adverse effects" OR poisoning OR toxicity	Limiters - Exclude MEDLINE records Search modes - Boolean/Phrase	111,797
19	S3 and S18	Limiters - Exclude MEDLINE records Search modes - Boolean/Phrase	71
20	Harm* OR MW "adverse effects" OR MW "chemically induced" OR MW "drug effects" OR MW mortality OR MW poisoning OR MW toxicity OR adverse effect* OR adverse event* OR adverse reaction* OR "Adverse Drug Reaction Reporting Systems" OR Accidents OR accident* OR "Drug Toxicity" OR "Drug Hypersensitivity" OR Death OR death* OR Suicide OR suicide OR suicidal* OR mania OR manic episode* OR overdos* OR self damage* OR self injur* OR "Self Injurious Behavior" OR self inflict*	Limiters - Exclude MEDLINE records Search modes - Boolean/Phrase	232,763
21	S3 and S20	Limiters - Exclude MEDLINE records Search modes - Boolean/Phrase	89
22	S19 or S21	Limiters - Exclude MEDLINE records Search modes - Boolean/Phrase	90
23	S22	Limiters - Exclude MEDLINE records; Human; Age Groups: Adolescent: 13-18 years, All Child; Language: English Search modes - Boolean/Phrase	4
24	S23	Limiters - Publication Type: Case Study, Editorial, Letter Search modes - Boolean/Phrase	0
25	S23 not S17	Search modes - Boolean/Phrase	3

#	Query	Limiters/Expanders	Results
26	S25	Limiters - Publication Type: Meta Analysis, Meta Synthesis, Systematic Review Search modes - Boolean/Phrase	0