Screening for Anxiety

Systematic Review for the Women's Preventive Services Initiative

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May 17, 2019 Updated Draft

INTRODUCTION

Anxiety disorders include several related conditions characterized by excessive, uncontrollable worry.[1] These include generalized anxiety disorder, panic disorder, social or school anxiety disorder, and other specific types.[1] Anxiety disorders cause significant impairment in daily activities, health, and function, including work and school responsibilities, and adversely impact well-being and social relationships.[2] Anxiety increases risk for major depression over the following year,[3] and is associated with unhealthy behaviors[4] and higher medical utilization.[5] Over 30 million Americans have anxiety during their lifetimes, and its economic impact has been estimated as $42 billion dollars per year.[6]

Anxiety disorders are the most frequent mental health disorders in the general population,[7] with approximately 31% of adults in the United States experiencing anxiety disorders during their lifetimes[8] and 19% over the past year.[9] These estimates are likely inaccurate because anxiety disorders are often undiagnosed.[2] Prevalence is higher among women compared with men (23% versus 14%).[9] Despite anxiety's high prevalence, only 43% of patients with anxiety receive treatment.[10] Other anxiety disorders, depression, and substance abuse are associated with generalized anxiety disorder. Anxiety is a common manifestation of additional underlying issues including PTSD, stress, bullying, sexual harassment and assault, and other experiences common in women.

The prevalence of anxiety disorders among U.S adolescents age 13 to 18 years is 32%, with higher rates for girls than boys (38% versus 26%).[7] Among adolescents with anxiety disorders, 8% meet Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for severe impairment. In children and adolescents, anxiety disorders are frequently associated with other conditions including depression, eating disorders, and attention-deficit/hyperactivity disorder.[11]

Generalized anxiety disorder is common in community and clinical settings[12] and is the focus of this systematic review. Patients with generalized anxiety disorder typically present with excessive worry about everyday situations. Disordered anxiety causes distress, is intrusive,

interferes with relationships and daily function, and is often associated with physical symptoms including restlessness, sleep disturbance, chronic headaches, gastrointestinal distress, or muscle tension.[1] Factors commonly associated with generalized anxiety disorder include female sex, unmarried status, lower education level, poor health, and presence of life stressors.[13] Generalized anxiety disorder can develop gradually and begin at any age, although the years of highest risk are between childhood and middle age. Nonetheless, generalized anxiety disorder is the most common anxiety disorder among older adults and is frequently associated with traumatic events such as a fall or acute illness.[8,10]

Although research on anxiety in women is limited, it suggests sex-specific features. Studies of anxiety during pregnancy describe the effects of elevated maternal cortisol on the developing fetus.[14] These include effects on sex-specific neonatal amygdala connectivity that manifests in behavioral problems of female offspring at age 2 years.[15] A longitudinal study of young girls indicated that early behaviors and emotional symptoms predicted anxiety diagnosis in adulthood.[16] Previous studies have shown associations of anxiety with environmental causes or triggers, particularly in teenage females. These include worries about school performance, concerns about appearance, earlier sexualization, changing media and consumer culture, and poor self-esteem.[17] In addition, females are more attentive to social and emotional experiences that increase stress.

Several brief screening instruments have been validated for identification of anxiety in primary care clinical settings. The diagnosis of generalized anxiety disorder is established by a clinical diagnostic interview using DSM-V criteria[1,18] (**Figure 1**). ICD-10 criteria are described in **Appendix 1**. Importantly, when evaluating a patient for suspected anxiety disorders, other potential medical conditions must be ruled out (e.g. endocrine, cardiopulmonary, neurologic diseases). Other psychiatric disorders including depression and bipolar disorder must be considered, in addition to the use of caffeine, medications (e.g., decongestants, albuterol, levothyroxine), addictive substances, or substance withdrawal.

Figure 1. DSM-V Criteria for Generalized Anxiety Disorder[19]

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B. The individual finds it difficult to control the worry.
C. The anxiety and worry are associated with three or more of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):
   Note: Only one item is required in children
   1. Restlessness or feeling keyed up or on edge
   2. Easily fatigued
   3. Difficulty concentrating or mind going blank
   4. Irritability
   5. Muscle tension
   6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
D. Anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E. The disturbance is not attributable to the physiological effects of a substance (e.g. a drug of abuse, a medication) or another medical condition (e.g. hyperthyroidism).
F. The disturbance is not better explained by another mental disorder, such as panic disorder.

Generalized anxiety disorder can be effectively treated with cognitive behavior therapy (CBT); other types of behavioral therapy, such as relaxation techniques; pharmacologic therapy; and combined regimens. Cognitive behavior therapy is frequently the initial therapy for most patients and can be as effective as medication.[20] Combining CBT with medication can be particularly effective for patients with moderate to severe symptoms. First line medications include selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and azapirone (buspirone). Tricyclic antidepressants and calcium modulators (pregabalin) are considered second line, while benzodiazepines are not recommended for treatment other than during an acute crisis.

Screening for anxiety has not been addressed by the U.S. Preventive Services Task Force (USPSTF), although screening for depression is recommended and has become standard practice in primary care.[21,22] Anxiety is often missed by clinicians because patients may be reluctant to discuss their distress, symptoms may be attributed to other causes, or anxiety may co-exist with other conditions, such as depression and substance use. Screening has the potential to identify previously unrecognized anxiety and related disorders, initiate individualized treatment to improve health and well-being, and prevent progression. An example of a clinical approach to screening is described below (**Table 1**).

Table 1. Clinical Approach to Screening for Anxiety

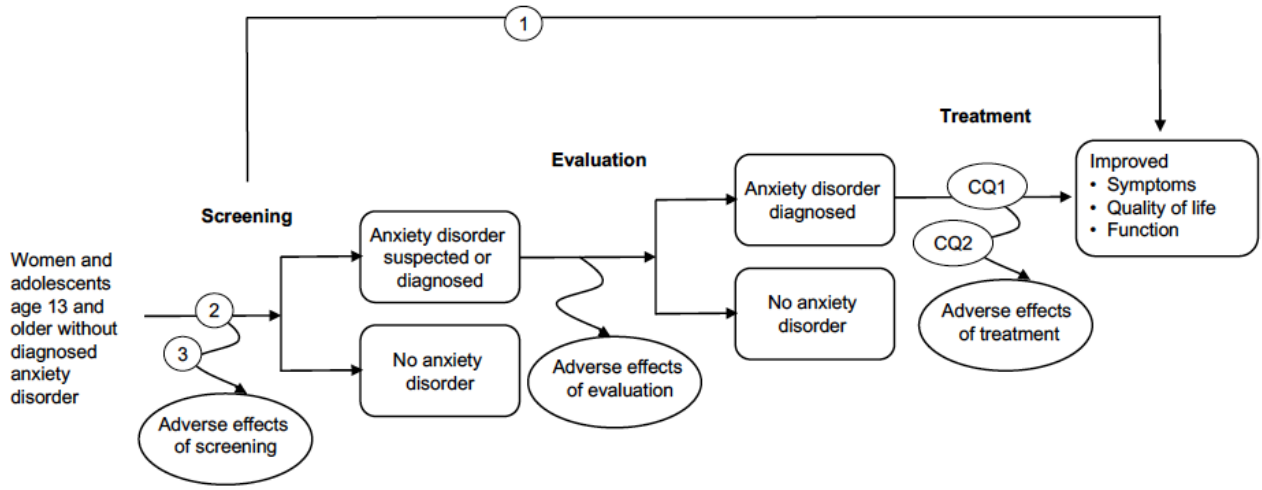
Screening		Interpretation & Diagnosis	Proposed Treatment Actions
Generalized Anxiety Disorder Scale-7 Score	Anxiety Severity		
0 - 5	None	Diagnostic criteria not met	None
6 - 10	Mild		Watchful waiting, repeat at follow up
11 - 15	Moderate	Diagnostic criteria met	Initiate cognitive behavioral therapy and consider pharmacotherapy
16 - 21	Severe		Initiate cognitive behavioral therapy and pharmacotherapy; consider referral to mental health specialist

The purpose of this systematic review is to evaluate evidence on the effectiveness of screening for generalized anxiety disorder in women and adolescent girls in improving symptoms, quality of life, and function; and the accuracy and potential harms of methods to screen for anxiety in routine clinical practice. While assessment of the effectiveness and harms of treatment are outside the scope of this review, this evidence is summarized contextually.

METHODS

The WPSI Advisory Group determined the scope and key questions for this review to inform the development of new screening recommendations. Investigators created an analytic framework outlining the key questions and patient populations, interventions, and outcomes (**Figure 2**). The target population includes women and adolescent girls age 13 and older without known current anxiety disorders.

Figure 2. Analytic Framework



Key Questions

1. In women and adolescents girls age 13 and older without currently diagnosed anxiety disorder, what is the effectiveness of screening and evaluation for anxiety to improve symptoms, quality of life, and function?
2. What is the accuracy of methods to screen for generalized anxiety disorder? How does accuracy vary between age, pregnancy status, social-demographic, and cultural groups; and among women with comorbid conditions or who use additional medications?
3. What are the potential adverse effects of screening for generalized anxiety disorder?

Contextual Questions

Two contextual questions are also included to provide additional information that could support the chain of evidence for screening. Contextual questions are not reviewed using systematic review methodology but are addressed using the strongest, most relevant evidence often from published systematic reviews or key studies. Contextual questions include:

1. What is the effectiveness of treatments for anxiety in improving symptoms, quality of life, and function?
2. What are the potential adverse effects of treatments for anxiety?

Literature Searches

A research librarian conducted electronic database searches in Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from 1996 to January 2019. Search strategies are provided in **Appendix 2**. Investigators also manually reviewed reference lists of relevant systematic reviews and articles.

Study Selection

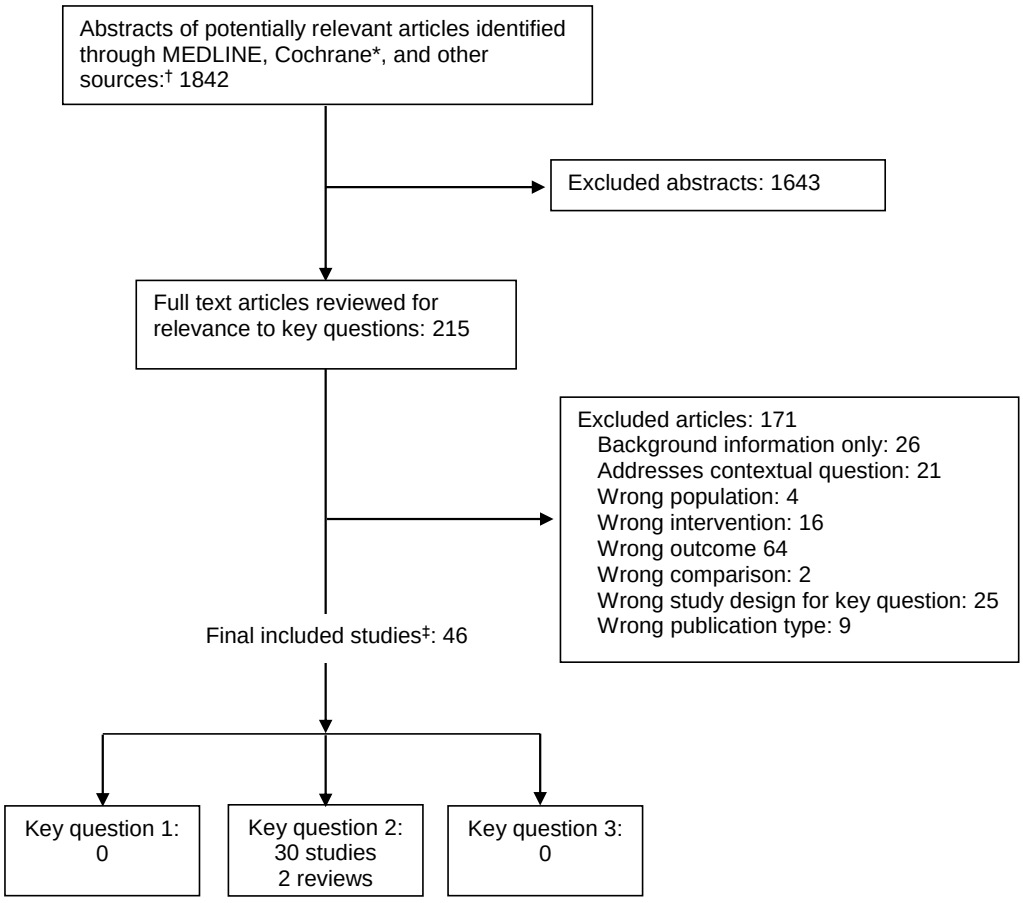
Investigators reviewed all titles and abstracts identified through searches and secondary referencing and determined inclusion based on pre-specified criteria defined by PICOTS components (population, intervention, comparator, outcome, timing, study design) (**Appendix 3**). Studies meeting eligibility criteria for possible inclusion by a reviewer at the abstract level subsequently underwent full-text review. Each full-text article was independently reviewed by two investigators based on the pre-specified eligibility criteria. All results were tracked in an EndNote® database (Thomson Reuters, New York, NY).

Studies were included that enrolled predominantly adolescent girls or adult women (>50% female participants) and were applicable to clinical practice in the United States. Findings related to population subgroups were specifically included when available. Randomized controlled trials (RCTs), large (>100) prospective cohort studies, diagnostic accuracy studies, and systematic reviews meeting eligibility criteria were included. Other study designs, such as case-control and modeling studies, were included when evidence from other study designs was lacking.

Investigators applied a best evidence approach when reviewing abstracts and selecting studies to include for this review that involves using the most relevant studies with the strongest methodology.[23-25] Disagreements regarding inclusion of studies were resolved by discussion and consensus. Results of the full text review were tracked in the EndNote® database, including reasons for exclusion. Results of searches and study selection are described in **Figure 3**.

For contextual questions on treatment (CQ 1, 2), studies were included that compared treatment against a placebo, no treatment, waitlist control, or usual care group. Treatment effectiveness outcomes included clinical response, reduction in anxiety symptoms or improvement in scores on validated scales, and quality of life measures. Multiple adverse effects outcomes were included as reported in studies.

Figure 3. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Identified from reference lists, hand searching, and other sources.
‡Studies that provided data and contributed to the body of evidence were included.

Data Extraction and Synthesis

For studies meeting inclusion criteria, data were abstracted into tables to summarize relevant information including characteristics of study populations, interventions, comparators, outcomes, study designs, settings, methods, and results. All data abstractions were reviewed for completeness and accuracy by a second investigator.

Predefined criteria were used to assess the quality of individual controlled trials, systematic reviews, observational studies, and diagnostic accuracy studies rating them as "good," "fair," or "poor" (**Appendix 4**).[26] Each study was independently rated for quality by two investigators and

disagreements were resolved by consensus. Studies were synthesized qualitatively. No statistical meta-analyses were conducted because of methodological and clinical heterogeneity.

Assessing Applicability

Applicability is defined as the extent to which the effects observed in published studies are likely to reflect the expected results when a specific intervention is applied to the population of interest under "real-world" conditions.[25] It is an indicator of the extent to which research included in a systematic review might be useful for informing clinical decisions. Factors important for understanding applicability were considered for each study including differences in the interventions, comparators, populations, and settings. Based on these factors, applicability was rated "high" or "low."

Establishing the Strength of Recommendations

The strength of evidence for each key question is assessed by using the approach described in the AHRQ Methods Guide.[27] Grades are based on study limitations, consistency, directness, precision, and reporting bias (**Appendix 5**).

RESULTS

Key Questions 1 and 3. Effectiveness and Harms of Screening for Anxiety

No studies met inclusion criteria that evaluated the overall effectiveness or harms of screening for anxiety in women or adolescent girls to reduce symptoms and increase function and well-being.

Key Question 2. Accuracy of Screening Methods

A total of 30 studies and 2 reviews that included 171 studies evaluated the diagnostic accuracy of methods to screen for generalized anxiety disorder in clinical practice and met inclusion criteria. Studies were conducted in either the general adult population[28-43] or among specific populations including adolescents,[44-48] pregnant and postpartum women,[49-55] and older adults.[56-58] All studies included at least 50% female participants. Included studies met criteria for good or fair quality.

Screening methods included various clinician or self-administered questionnaires addressing symptoms of anxiety designed for use in clinical practice (**Table 2; Appendix 6**). Responses were typically scored using a Likert scale or other point system. Diagnostic accuracy measures were determined by comparing scores against reference standards that generally included clinical diagnosis using DSM criteria. Results were expressed as AUC c-statistics, sensitivity and specificity values, or positive and negative likelihood ratios.

Table 2. Instruments Included in Studies

Abbreviation	Screening Instrument	Study (author, year)
BAI	Beck Anxiety Inventory	Leyfer, 2006[37] Dennis, 2007[59] O'Hara, 2012[52]
BSI-A	Brief Symptom Inventory-18	Wetherell, 2007[58]
CES-D	Center for Epidemiologic Studies- Depression Scale	Dozeman, 2011[60] Dierker, 2001[47]
CIDI	Composite International Diagnostic Interview	Austin, 2010[61] Rowe, 2008[62]
DASS-21	Depression, Anxiety, and Stress Scale 21	Somerville, 2014[54]
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders	Newman, 2002[40] Houston, 2011[34]
DUKE-AD	Duke Anxiety-Depression Scale	Parkerson, 1997[41]
EK10	Extended Kessler-10	Donker, 2010[30]
EPDS	Edinburgh Postnatal Depression Scale	Austin, 2010[61] Matthey, 2013[49] McDonald, 2012[50] Meades, 2011[51] O'Hara, 2012[52] Petrozzi, 2013 [63] Rowe, 2008[62] Simpson, 2014[53] Somerville, 2014[54] Tendais, 2014[55]
FEAR	Frequency of anxiety; enduring nature of anxiety; alcohol or sedative use; restlessness or fidgeting	Krasucki, 1999[56]
GAD-2	Generalized Anxiety Disorder Scale-2 items	Donker, 2011[31] Garcia-Campayo, 2012[33]
GAD-7	Generalized Anxiety Disorder Scale-7 items	Batterham, 2013[64] Donker, 2011[31] Munoz-Navarro, 2017[39] Spitzer, 2006[43] Vasiliadis, 2015[57] Simpson, 2014[53]
GAD-Q-IV	Generalized Anxiety Disorder Questionnaire	Moore, 2014[38] Newman, 2002[40] Roemer, 1995[65]
GAD-SI	Single item from the GAD-7	Donker, 2011[31]
GADSS	Generalized Anxiety Severity Disorder	Weiss, 2009[66]
GAS/GAD	Goldberg Anxiety and Depression Scales	Kiely, 2015[35]
GHQ	General Health Questionnaire	Meades, 201 [51]
HADS	Hospital Anxiety and Depression Scale	Dennis, 2007[59] Jomeen, 2003[67] Wetherell, 2007[58] Matthey, 2013[49] Meades, 2011[51]
K10	Kessler Psychological Distress Scale	Donker, 2010[30] Vasiliadis, 2015[57]
MASC	Multidimensional Anxiety Scale for Children	Dierker, 2001[47]
MCS-12	Mental Health Component Summary Scale Web-based depression and anxiety test	Kiely, 2015[35]
MINI	Mini-International Neuropsychiatric Interview	Grant, 2008[68]
PASS	Perinatal Anxiety Screening Scale	Somerville, 2014[54]
PDI-4	Provisional Diagnostic Instrument	Houston, 2011[34]
PDSQ	Psychiatric Diagnostics Screening Questionnaire	Leung, 2017[69]
PHQ-4	Patient Health Questionnaire for depression and anxiety (4 items)	Kroenke, 2009[36] Cano-Vindel, 2018[70]
PHQ-9	Patient Health Questionnaire for depression and anxiety (9 items)	Kiely, 2015[35]

Abbreviation	Screening Instrument	Study (author, year)
PSS	Cohen Perceived Stress Scale	McDonald, 2012[50]
PSWQ	Penn State Worry Questionnaire	Behar, 2003[28]
RCADS	Revised Child Anxiety and Depression Scale	Piqueras, 2017[48]
RCMAS	Revised Children's Manifest Anxiety Scale	Dierker, 2001[47]
SCARED	Screen for Child Anxiety Related Emotional Disorders	Birmaher, 1997[44] Birmaher, 1999 [45] Bodden, 2009[46] Crocetti, 2009[71] Hale, 2013[72]
SCID	Structured Clinical Interview for DSM-IV	Farvolden, 2003[32] O'Hara, 2012[52]
STAI	State Trait Anxiety Inventory	Dennis, 2007[59] Grant, 2008[68] McDonald, 2012[50] Meades, 2011[51] Somerville, 2014[54] Tendais, 2014[55]
VAS	Visual Analogue Scale	Dennis, 2007[59]
WB-DAT	Web-based Depression and Anxiety Test	Farvolden, 2003[32]
WSQ	Web Screening Questionnaire	Donker, 2009[29]

Studies of Screening in Adolescents

Four studies[44-47] and one systematic review[48] of screening methods for adolescents met inclusion criteria (**Table 3**). Screening methods included four variations of Screen for Child Anxiety Related Emotional Disorders (SCARED)[44-46]; the Revised Children's Manifest Anxiety Scale (RCMAS)[47]; the Multidimensional Anxiety Scale for Children (MASC) [47]; and the Revised Child Anxiety and Depression Scale (RCADS). [48]

The original SCARED instrument includes 38-items with five subscales specific for panic disorder, generalized anxiety disorder, separation anxiety disorder, social anxiety, and school anxiety. Several variations exist including 41-item, 71-item, and 5-item versions that were evaluated in the included diagnostic accuracy studies. The original SCARED instrument demonstrated sensitivity of 72% and specificity 64% in a study of adolescents age 9 to 18 years in a mood/anxiety disorders clinic.[44] A study comparing two versions of SCARED in adolescents age 9 to 19 years reported sensitivity and specificity of 71% and 67% for the 41-item version, and 74% and 73% for the 5-item version.[45] In another study, the 71-item version demonstrated sensitivity 64% and specificity 69% in adolescents age 8 to 18 years.[46]

The RCMAS and MASC instruments were evaluated in a study of 632 ninth graders enrolled in five high schools across the United States. The RCMAS is a 37-item self-report measure using yes or no responses to calculate a composite anxiety score; while the 39-item MASC rates the frequency of symptoms on a four-point scale. Results indicated AUC values for specifically for girls of 0.62 for RCMAS and 0.82 for MASC.[47]

A systematic review of 146 studies evaluated RCADS, a 47-item instrument with six subscales for separation anxiety disorder, social phobia, generalized anxiety disorder, panic disorder, obsessive compulsive disorder, and major depressive disorder.[48] Studies included children and adolescents 6 to 18 years old, and combined results were reported as a reliability measure (0.91; 95% CI 0.90 to 0.92).

Table 3. Studies of Screening Instruments Developed for Children and Adolescents

Screening Instrument	Description	Study (author, year)	Participants	Reference standard	Performance characteristics (95% CI)
SCARED[44]	38-items in 5 subscales: panic disorder, generalized anxiety disorder, separation anxiety disorder, social anxiety, school anxiety.	Birmaher, 1997[44]	341 adolescents 9 to 18 years old in a mood/anxiety disorders clinic	Either clinical interview using DSM-IV diagnosis criteria or K-SADS-P diagnosis	Sensitivity: 72% Specificity: 64%
SCARED-41[45]	41-item scale; addition of 3 items to the social phobia subscale of the SCARED scale.	Birmaher, 1999[45]	190 adolescents 9 to 19 years old in a mood/anxiety disorders clinic	Comprehensive symptom checklist for DSM-IV diagnostic criteria	Sensitivity: 71% Specificity: 67%
SCARED-71[46]	71-item scale; adds 3 additional subscales to the SCARED scale: specific phobia, obsessive-compulsive disorder, and post-traumatic stress disorder.	Bodden, 2009[46]	176 adolescents 8 to 18 years old; clinically anxious cases and controls	ADIS-C and ADIS-P	Sensitivity: 64% Specificity: 69%
5-item SCARED[45]	A shorter version of the SCARED-41; includes 1 item from each subscale that best discriminates between anxious and non-anxious respondents.	Birmaher, 1999[45]	190 adolescents 9 to 19 years old in a mood/anxiety disorders clinic	Comprehensive symptom checklist for DSM-IV diagnosis criteria	Sensitivity: 74% Specificity: 73%
RCMAS[73]	37-item self-report measure using yes or no responses to each statement. A composite anxiety score is calculated by summing the number of yes responses (range 0–28).	Dierker, 2001[47]	632 9th graders enrolled in 5 high schools across the United States	Diagnostic interview modules selected from the DSM-IV diagnosis criteria	AUC for girls: 0.62
MASC[74]	39-item rating scale; respondents rate the frequency of symptoms on a four-point scale: 0=never; 1=rarely; 2=sometimes; and 3=often.	Dierker, 2001[47]	632 9th graders enrolled in 5 high schools across the United States	Diagnostic interview modules selected from the DSM-IV diagnosis criteria	AUC for girls: 0.82
RCADS[75]	47 items in 6 subscales: separation anxiety disorder, social phobia, generalized anxiety disorder, panic disorder, obsessive compulsive disorder, and major depressive disorder.	Piqueras, 2017;[48] 146 studies in systematic review	88,648 children and adolescents 6 to 18 years old	Not reported, multiple studies	Reliability: 0.91 (0.90 to 0.92)*

Abbreviations: ADIS-C= Anxiety Disorder Interview Schedule-Child scale; ADIS-P=Anxiety Disorder Interview Schedule-Parent scale ; AUC=area under the receiver operating characteristic curve; CI=confidence interval; DSM=Diagnostic and Statistical Manual of Mental Disorders; GAD=generalized anxiety disorder; K-SADS-P= Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present Episode; MASC=Multidimensional Anxiety Scale for Children; RCADS=Revised Child Anxiety and Depression Scale; RCMAS=Revised Children's Manifest Anxiety Scale; SCARED=Screen for Child Anxiety Related Emotional Disorders.

*Determined by Cronbach's alpha measure to estimate internal consistency of RCADS.

Studies of Screening in the General Adult Population

Seventeen studies of 11 screening methods for adults in the general population met inclusion criteria (**Table 4**). Screening methods included four variations of the Generalized Anxiety Disorder (GAD) instrument[31,33,36,38-40,43,70]; the Penn State Worry Questionnaire (PSWQ)[28]; Web Screening Questionnaire (WSQ)[29]; Kessler-10 (K10) and extended version (EK-10) [30]; Web-Based Depression and Anxiety Test (WB-DAT)[32]; Provisional Diagnostic Instrument (PDI-4)[34]; Goldberg Anxiety Scale (GAS)[35]; Beck Anxiety Inventory (BAI)[37]; Duke Anxiety-Depression Scale (DUKE-AD)[41]; and 2 screening questions.[42]

The GAD-7 is the anxiety module of the Patient Health Questionnaire (PHQ) that assesses anxiety symptoms over the last 2 weeks. Three studies of the GAD-7 demonstrated sensitivities of 87% to 89%, specificities of 50% to 82%, and AUC 0.77 using a cut-point of 10.[31,39,43] The GAD-2, a shorter version, was evaluated in four studies indicating sensitivity from 70% to 91.5%, specificity 61% to 86%, and AUC 0.78 to 0.94.[31,33,36,70] A study of 2149 primary care patients reported an AUC value for GAD-2 of 0.908.[36] Studies of the GAD-Q-IV, an updated 9-item version, indicated sensitivity 97%, specificity 86%, and AUC 0.85 when using a DSM based algorithm[38]; and sensitivity ranging from 83% to 89% and specificity from 72% to 89% when using a cut-point of 7.6.[38,40]

The diagnostic accuracies of additional methods were reported in single studies. Of these, the PSWQ, WSQ, Kessler-10 and EK-10, PDI-4, GDS, GAS, BAI, DUKE-AD, and 2 screening questions demonstrated moderate to high performance measures, while the WB-DAT indicated lower performance.

Table 4. Studies of Screening Instruments in Adults

Screening Instrument	Description	Study (author, year)	Participants	Reference Standard	Performance Characteristics (95% CI)
GAD-2	GAD-2 is derived from the anxiety module of the Patient Health Questionnaire (PHQ). Assesses anxiety symptoms over the last 2 weeks: • Feeling nervous, anxious, or on edge • Not being able to stop or control worrying • Feeling down, depressed, or hopeless • Little interest or pleasure in doing things	Donker, 2011[31]	502 adults age 18 to 80 compared with 20 psychology students; web-based (57% female)	DSM-IV CIDI GAD	Cutoff 3 Sensitivity: 70%; Specificity: 76% AUC: 0.78 (0.69 to 0.86)
		García-Campayo, 2012[33]	220 adults age >18 (72% female)	HAM-A, HADS, and WHODAS II	Cutoff 3 Sensitivity: 91.5%; Specificity: 85.8% AUC: 0.937
		Kroenke, 2009[36]	2149 primary care patients (66% female)	Structured interview using DSM-IV criteria	AUC: 0.908 (0.876 to 0.940)
		Cano-Vindel, 2018 [70]	1052 primary care patients (77% female)	SCID-I	Cutoff 3 Sensitivity: 88%; Specificity: 61% AUC >0.85
GAD-7	GAD-7 is the anxiety module of the Patient Health Questionnaire (PHQ). Assesses anxiety symptoms over the last 2 weeks: • Feeling nervous, anxious or on edge • Not being able to stop or control worrying • Worrying too much about different things • Trouble relaxing • Being so restless that it's hard to sit still • Becoming easily annoyed or irritable • Feeling afraid as if something awful might happen	Donker, 2011[31]	502 adults age 18 to 80 compared with 20 undergraduate psychology students; web-based (57% female)	DSM-IV CIDI GAD	Cutoff 10 Sensitivity: 87 to 89% Specificity: 50 to 82% AUC: 0.77 (0.68 to 0.85)
		Munoz-Navarro, 2017[39]	178 adults age 18 to 65 in primary care (71% female)	CIDI for DSM-IV	Cutoff 10 Sensitivity: 87%; Specificity: 78%
		Spitzer, 2006[43]	2740 adults in primary care clinics; mean age 47 (18-95 years) (65% female)	Structured interviews for 965	Cutoff 10: Sensitivity: 89%; Specificity: 82%
GAD-Q-IV	The fourth edition of the Generalized Anxiety Disorder Questionnaire (GAD-Q-IV) is a 9-item self-report measure.	Moore, 2014[38]	104 adults in primary care (69% female)	SCID-IV	AUC: 0.85 (0.76 to 0.93) DSM-based algorithm Sensitivity: 97%; Specificity: 86% Cutoff 7.6 Sensitivity: 89%; Specificity: 72%
		Newman, 2002[40]	143 undergraduates (80% female)	DSM structured interview	Sensitivity: 83%; Specificity: 89%

Screening Instrument	Description	Study (author, year)	Participants	Reference Standard	Performance Characteristics (95% CI)
PSWQ	A 16-item measure designed to assess the pathological worry characteristic of GAD. Including the generality, excessiveness, and uncontrollability of worry without focusing on particular domains of worry.	Behar, 2003[28]	2449 young adults (71% female)	GAD-Q-IV	Cutoff 62 Sensitivity: 75%; Specificity: 86%
WSQ	Includes 15 items to screen for depression, GAD, panic disorder with and without agoraphobia, social phobia, specific phobia, OCD, PTSD, and alcohol abuse/dependence.	Donker, 2009[29]	502 adults age 18 to 80 recruited from the internet (57% female)	CIDI diagnosis with live phone interviews	Cutoff ≥10 Sensitivity: 89%; Specificity: 82%
Kessler-10 (K10), EK-10 (extended version)	K-10: 10 questions; screens broadly for psychological distress. EK-10: Extended with five additional questions focusing on anxiety symptoms.	Donker, 2010[30]	1607 adults in primary care age 18 to 65 years (69% female)	CIDI interview, DSM-IV diagnosis	K10-20 Sensitivity: 94%, Specificity: 67% EK10-20 Sensitivity: 95%; Specificity: 61%
WB-DAT	11 broad preliminary questions; final report based on algorithm response to specific questions.	Farvolden, 2003[32]	32 adults (59% female)	SCID-I/P interview	Sensitivity: 63%; Specificity: 94%
PDI-4	17-item instrument for provisional differential diagnosis with 4 items specific for anxiety.	Houston, 2011[34]	24 adults in (>60% female)	SCID/ACDS assessment, DSM-IV	Sensitivity: 83%; Specificity: 75% Follow up with GAD-7 Sensitivity: 89%: Specificity: 82%
Goldberg Anxiety Scales (GAS)	Asks respondents whether they experienced 9 anxiety symptoms over the past 4 weeks. Scores are summed to give a maximum total of 9 on each scale.	Kiely, 2015[35]	1015 community adults (ages 32 to 36 and 52 to 58) (59% female)	CIDI	Cutoff 7 Sensitivity: 84%; Specificity: 86% AUC: 0.8957
Beck Anxiety Inventory (BAI)	21-item self-report questionnaire that lists symptoms of anxiety. The respondent is asked to rate how much each symptom has bothered them in the past week.	Leyfer, 2005[37]	193 adults in the general population (76% female)	ADIS-IV	Cutoff 3.5 Sensitivity: 75%; Specificity: 73%
DUKE-AD	Includes two items for negative affect (feeling depressed or sad, nervousness), two for somatic symptoms (trouble sleeping, getting tired easily), two for self-esteem (give up easily, uncomfortable being around people), and one for cognition (difficulty concentrating).	Parkerson, 1997[41]	481 adults in primary care age 18 to 64 (72% female)	DSM	Sensitivity: 71.4%; Specificity: 59.2% AUC: 0.723

Screening Instrument	Description	Study (author, year)	Participants	Reference Standard	Performance Characteristics (95% CI)
2 screening questions	Screening question for anxiety: "During the past month have you been worrying a lot about everyday problems?" If patients answered yes, then asked to complete a second question: "Is this something with which you would like help?"	Puddifoot, 2007[42]	982 adults (72% female)	HADS anxiety score >11	Two screening questions Sensitivity: 58%; Specificity: 87% Worry question alone Sensitivity: 76%; Specificity: 82%

Abbreviations: ADIS-IV=Anxiety Disorders Interview Schedule; AUC=area under the receiver operating characteristic curve; CI=confidence interval; CIDI=Composite International Diagnostic Interview; DSM=Diagnostic and Statistical Manual of Mental Disorders; DUKE-AD=Duke Anxiety-Depression Scale; GAD=generalized anxiety disorder; GAS=Goldberg Anxiety Scale; HADS=Hospital Anxiety and Depression Scale; HAM-A=Hamilton Anxiety Scale; OCD=obsessive compulsive disorder; PDI-4= Provisional Diagnostic Instrument-4; PHQ=Patient Health Questionnaire; PSWQ=Penn State Worry Questionnaire; PTSD=posttraumatic stress disorder; SCID/ACDS=Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition axis I disorders and the Adult ADHD Clinician Diagnostic Scale version 1.2; SCID-IV=Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition axis I disorders; WB-DAT=Web-Based Depression and Anxiety Test; WHODAS II=World Health's Organization Disability Assessment Scale; WSQ=Web Screening Questionnaire.

Studies of Screening in Pregnant and Postpartum Women

A total of 6 studies and 1 review of 25 studies evaluating the diagnostic accuracy of 11 screening methods met inclusion criteria (**Table 5**). These include two versions of the Edinburgh Postnatal Depression Scale (EPDS)[49,50,53,55]; the Hospital Anxiety and Depression Scale-anxiety subscale (HADS-A)[49,51]; Pregnancy-Related Thoughts (PRT)[49]; Pregnancy Related Anxiety Questionnaire-Revised (PRAQ-R)[49]; Matthey Generic Mood Question (MGMQ)[49]; McDonald Prenatal Screening Tool[50]; State Trait Anxiety Inventory (STAI)[51,55]; General Health Questionnaire (GHQ)[51]; Generalized Anxiety Disorder 7-item scale (GAD-7)[53]; Perinatal Anxiety Screening Scale (PASS)[54]; and Beck Anxiety Inventory (BAI-Subj).[52]

The EPDS is a 10-item self-reported measure commonly used in the United States to assess pregnant and postpartum women for symptoms of emotional distress during the past 7 days. Results of three studies varied depending on cut-points and pregnancy status. The AUC value was 0.73 (95% CI 0.62 to 0.83) in a study of pregnant women in the community[50], and 0.62 in a study of pregnant women referred for psychiatric consultation.[53] Sensitivity ranged from 41% to 89% and specificity from 27% to 88% across three studies. Two studies of a 3-item variation of the EPDS indicated AUC 0.69; sensitivity 54% to 68%; and specificity 63%.[49,53]

Several studies of pregnant and postpartum women evaluated instruments commonly used in general populations. In a study of the GAD-7 using a cut-point of 10, sensitivity was 76.0% and specificity 51.5%.[53] Studies using variations of the GHQ indicated sensitivity from 75% to 83%, and specificity from 71% to 89%.[51] The STAI demonstrated sensitivity of 66% to 81%, and specificity 67% to 80% in two studies [51,55] with various cut-points.

The diagnostic accuracies of additional methods were reported in single studies. Of these, the MGMQ,[49] McDonald Prenatal Screening Tool,[50] PASS,[54] and BAI-Subj[52] demonstrated moderate to high performance measures, while the PRT[49] and PRAQ-R,[49] indicated lower performance.

Table 5. Studies of Screening Instruments in Pregnant and Postpartum Women

Screening Instrument	Description	Study (author, year)	Participants	Reference Standard	Performance Characteristics (95% CI)
EPDS[76]	10-item self-report measure assessing pregnant and postpartum women for symptoms of emotional distress during the past 7 days.	McDonald, 2012[50]	567 pregnant women (<24 weeks) from the community	STAI-state anxiety scale	Sensitivity: 41% (27 to 61) Specificity: 88% (82 to 91) PPV: 0.34 (0.20 to 0.49) NPV: 0.91 (0.87 to 0.95) AUC: 0.73 (0.62 to 0.83)
		Simpson, 2014[53]	155 pregnant and 85 postpartum women mean age 30.5 years referred for psychiatric consultation	DSM-IV diagnosis	Cutoff 10 to 13 Sensitivity: 77.3 to 89.3% Specificity: 26.7 to 40.3% PPV: 0.36 to 0.38 NPV: 0.79 to 0.84 AUC for GAD: 0.62 AUC for GAD and MDD: 0.68
		Tendais, 2014[55]	35 pregnant and postpartum women mean age 28 years in obstetrics outpatient unit	SCID diagnosis	Cutoff >9 during pregnancy Sensitivity: 73.7% (56.9 to 86.6) Specificity: 70.0% (60.5 to 78.4) PPV: 0.46 (0.33 to 0.59) NPV: 0.89 (0.80 to 0.94) Cutoff >7 postpartum Sensitivity: 78.3% (56.3 to 92.5) Specificity: 81.6% (71.0 to 89.5) PPV: 0.56 (0.38 to 0.74) NPV: 0.93 (0.83 to 0.98)
EDS-3a[76,49]	3 items derived from the EPDS. Each item has 4 response options; total scores on the anxiety subscale range from 0 to 9; higher scores indicate increased anxiety.	Matthey, 2013[49]	391 pregnant women mean age 28.8 years attending first prenatal visit	MINI diagnosis	Sensitivity: 54%
		Simpson, 2014[53]	155 pregnant and 85 postpartum women mean age 30.5 years referred for psychiatric consultation	DSM-IV diagnosis	Sensitivity: 68.0%; Specificity: 63.5% PPV: 0.46; NPV: 0.81 AUC for GAD: 0.69 AUC for GAD and MDD: 0.67
HADS-A[77]	7 items about general anxiety over the past 7 days. Total scores range from 0 to 21; higher scores indicate increased anxiety.	Matthey, 2013[49]	391 pregnant women mean age 28.8 years attending first prenatal visit	MINI diagnosis	Sensitivity: 35%
		Meades, 2011 (SR)[51]	441 pregnant women	MINI plus, semi-structured interview, or SCID diagnosis	Sensitivity: 92.9%; Specificity: 90%

Screening Instrument	Description	Study (author, year)	Participants	Reference Standard	Performance Characteristics (95% CI)
PRT[78]	10 items about concerns regarding the health of the baby, labor and delivery, and caring for the baby over the past 7 days. Each item has 4 response options; total scores range from 10 to 40; higher scores indicate increased anxiety.	Matthey, 2013[49]	391 pregnant women mean age 28.8 years attending first prenatal visit	MINI diagnosis	Sensitivity: 20%
PRAQ-R[79]	10-item questionnaire with 3 domains using a 5-point scale. Total scores range from 10 to 50; higher scores indicate increased anxiety.	Matthey, 2013[49]	391 pregnant women mean age 28.8 years attending first prenatal visit	MINI diagnosis	Sensitivity: 33%
MGMQ[49]	1 question: In the last 2 weeks have you felt very stressed, anxious or unhappy, or found it difficult to cope, for some of the time? Follow-up question for those answering "Yes" or "Possible:" How bothered have you been by these feelings?	Matthey, 2013[49]	391 pregnant women mean age 28.8 years attending first prenatal visit	MINI diagnosis	Sensitivity: 80%
McDonald Prenatal Screening Tool	Includes items relating to depression, stress, abuse history, and poor relationship quality.	McDonald, 2012[50]	567 pregnant women <24 weeks	STAI-state anxiety scale	Sensitivity: 44% (29 to 60) Specificity: 88% (82 to 91) PPV: 0.34 (0.20 to 0.49) NPV: 0.91 (0.87 to 0.95) AUC: 0.71 (0.61 to 0.82)
STAI [80]	Consists of 2 subscales with 20 items each. Measures anxiety at this moment or in general. Respondents endorse items on a 4-point scale.	Meades, 2011 (SR)[51]	100 pregnant women	MINI plus, semi-structured interview, or SCID diagnosis	Cutoff >40 Sensitivity: 80.95%; Specificity: 79.75% PPV: 0.52; NPV: 0.94
		Tendais, 2014[55]	35 pregnant women mean age 28 years	SCID diagnosis	Cutoff >40 during pregnancy Sensitivity: 65.7% (47.8 to 80.9) Specificity: 67.3% (57.8 to 75.8) PPV: 0.38 (0.26 to 0.52) NPV: 0.86 (0.77 to 0.93) Cutoff >34 postpartum Sensitivity: 71.4% (66.1 to 99.8) Specificity: 67.1% (56.0 to 76.9) PPV: 0.26 (0.13 to 0.43) NPV: 0.93 (0.84 to 0.98)

Screening Instrument	Description	Study (author, year)	Participants	Reference Standard	Performance Characteristics (95% CI)
GHQ[81-83]	Asks how the respondent has felt recently using 4-point response scales; higher scores indicate increased likelihood of disorder. The GHQ has 4 different versions (60-item, 30- item; 28-item and 12-item versions) and can be scored 4 different ways.	Meades, 2011 (SR)[51]	2525 pregnant women	Clinical interview schedule, SCID, or ICD-o diagnosis; SADS, PAS, or ICD-9	GHQ-30 (3 studies) Sensitivity: 77 to 83% Specificity: 71 to 89% PPV: 0.37 to 0.53; NPV: 0.90 to 0.97 GHQ-28 (2 studies) Sensitivity: 75%; 82% Specificity: 83%; 85% PPV: 0.46; 0.53; NPV: 0.95; 0.96 GHQ-12 (2 studies) Sensitivity: 83%; 81% Specificity: 80%; 81%
GAD-7[43]	7 self-rated items are each scored from 0 to 3; total score ranges from 0 to 21.	Simpson, 2014[53]	155 pregnant and 85 postpartum women mean age 30.5 years	DSM-IV diagnosis	Cutoff >10 Sensitivity: 76.0%; Specificity: 51.5% PPV: 0.42; NPV: 0.83 Cutoff >13 Sensitivity: 61.3%; Specificity: 72.7% PPV: 0.51; NPV: 0.81 AUC for GAD: 0.71 AUC for GAD and MDD: 0.74
PASS	38-item self-report questionnaire with a 4-point Likert scale assessing the frequency of symptoms.	Somerville, 2014[54]	53 pregnant and postpartum women ≥18 years in prenatal clinic	ICD-10 diagnosis	Sensitivity: 70%; Specificity: 30% AUC: 0.7 (SE 0.04)
BAI-Subj [84]	Assesses 21 affective and somatic symptoms of anxiety on a 4-point scale. The 6-item Subjective subscale (BAI-Subj) was used in the study because it most clearly represents general anxiety symptoms.	O'Hara, 2012[52]	353 postpartum women mean age 27 years; mean 21 weeks postpartum	SCID diagnosis	Cutoff >4 Sensitivity: 76%; Specificity: 71% PPV: 0.31 AUC: 0.78 Cutoff >6 Sensitivity: 56%; Specificity: 82% PPV: 0.35

Abbreviations: AUC=area under the receiver operating characteristic curve; BAI=Beck Anxiety Inventory; CI=confidence interval; DSM=Diagnostic and Statistical Manual of Mental Disorders; EDS-3a=Edinburgh Depression Scale-anxiety subscale; EPDS=Edinburgh Postnatal Depression Scale; GAD=generalized anxiety disorder; GAD-7=Generalized Anxiety Disorder 7-item scale; GHQ=General Health Questionnaire; HADS-A=Hospital Anxiety and Depression Scale-anxiety subscale; MINI-Mini-International Neuropsychiatric Interview; MGMQ=Matthey Generic Mood Question; NPV=negative predictive value; PASS=Perinatal Anxiety Screening Scale; PPV=positive predictive value; PRAQ-R=Pregnancy Related Anxiety Questionnaire-Revised; PRT=Pregnancy-Related Thoughts; SCID=Structured Clinical Interview for DSM-IV; SE=standard error; STAI=State Trait Anxiety Inventory.

Studies of Screening in Older Adults

Three studies evaluated five screening methods in adults age 60 years and older (**Table 6**). These included the Anxiety Disorder Scale (ADS) and FEAR instruments specific to older adults[56]; and the GAD-7,[57] Hospital Anxiety and Depression Scale (HADS),[58] and Brief Symptom Inventory (BSI-18)[58] that are used in general adult populations.

The ADS was developed as a survey instrument for detecting anxiety disorders in individuals age 65 and older and includes 11 items in a generalized anxiety subscale. The FEAR instrument is a 4-item version of the ADS. A study of older adults in primary care settings indicated 85% sensitivity and 71% specificity for the ADS; and 74% sensitivity and 85% specificity for FEAR.[56]

Additional studies of older patients in primary care clinics indicated AUC values of 0.695 for GAD-7[57]; 0.80 for HADS[58]; and 0.573 for BSI-18.[58]

Table 6. Studies of Screening Instruments in Older Adults

Screening Instrument	Description	Study (author, year)	Participants	Reference Standard	Performance Characteristics
ADS FEAR	ADS: Developed as a survey instrument for detecting anxiety disorders in a community sample of individuals age 65 and over. Includes 11 items in a generalized anxiety subscale. FEAR: 4-item version of the ADS.	Krasucki, 1999[56]	88 adults age >65 in primary care settings (64% female)	Clinical Interview, ICD-10 diagnosis	ADS: Sensitivity: 85% Specificity: 71% FEAR: Sensitivity: 74% Specificity: 85%
GAD-7	Evaluates anxiety symptoms using a 4-point Likert scale; total scores range from 0 to 21. Higher scores indicate higher severity, while scores below 5 indicate minimal anxiety.	Vasiliadis, 2015[57]	1775 adults age ≥65 in primary care clinics (57% female)	DSM-IV diagnosis, in person interview	Cutoff 5: Sensitivity: 71% Specificity: 57% AUC 0.695
HADS BSI-18	HADS: 14-item questionnaire to detect anxiety and depression in the general medical outpatient population. BSI-18: Includes 6 items scored on a 5-point Likert scale. Includes items assessing depression and anxiety.	Wetherell, 2007[58]	68 adults >60 in primary care clinics (67% female)	ADIS-IV interview, DSM diagnosis	HADS: Sensitivity: 97% Specificity: 67% AUC 0.80 BSI-18: AUC 0.573, SE 0.092

Abbreviations: ADIS-IV=Anxiety Disorders Interview Schedule; ADS=Anxiety Disorder Scale; AUC=area under the receiver operating characteristic curve; BSI=Brief Symptom Inventory; DSM=Diagnostic and Statistical Manual of Mental Disorders; FEAR=Frequency of anxiety; Enduring nature of anxiety; Alcohol or sedative use; Restlessness or fidgeting; GAD=generalized anxiety disorder; HADS=Hospital Anxiety and Depression Scale; ICD=International Statistical Classification of Diseases; SE=standard error.

Contextual Question 1. Effectiveness of Treatments for Anxiety

The effectiveness of treatments for anxiety has been evaluated by studies that are summarized in several systematic reviews of psychological[85-88] and pharmacological treatments.[89-95,97, 98]

Psychological Therapy

Cognitive behavioral therapy (CBT) is the first line psychological therapy for GAD and usually includes a combination of psychoeducation, worry exposure, relaxation, applied relaxation, problem-solving, cognitive re-structuring, and interpersonal psychotherapy.[96] Therapy can be delivered individually or as a group, face-to-face, over the internet, or via the telephone.

Four systematic reviews evaluate the effectiveness of psychological therapies for anxiety disorders (**Table 7**). Two high quality Cochrane reviews, one of therapies for children and adolescents,[87] and the other for adults,[86] compared psychological therapies with waitlist controls, active treatment arms (either another psychological therapy or pharmacotherapy), usual care, and psychological placebos. Two additional high quality reviews of adults compared computer or internet delivered CBT with face-to-face therapy, an alternate media-delivered intervention, waitlist control, psychological placebos, or usual care.[85,88]

Adolescents

A Cochrane review of psychological therapies in children and adolescents included 42 studies (41 in meta-analysis) enrolling 1806 participants.[87] Most studies enrolled children ages 7 to 14 years old, although some included up to age18 years. Most studies were conducted in research settings, such as university outpatient clinics, although some were conducted in community clinics and inner city schools. Symptoms of anxiety were assessed using the Revised Children's Manifest Anxiety Scale (RCMAS); Fear Survey for Children Revised (FSSC-R); Social Anxiety Scale for Adolescents (SAS-A); Social Phobia and Anxiety Inventory for Children (SPAI); Mood and Anxiety Symptom Scale (MASQ); Spence Child Anxiety Scale, child and parent versions (SCAS); Child Behavior Checklist (CBCL); and the Clinical Global Impressions Scale.

In a meta-analysis of studies, anxiety remission was improved for CBT compared with waitlist controls (odds ratio [OR] 7.85; 95% CI 5.31 to 11.60; 25 studies). Results were similar for individual and group CBT compared with waitlist controls (individual therapy OR 7.92; 95% CI 3.37 to 18.63; 7 studies; group therapy OR 7.86; 3.83 to 16.12; 13 studies). Differences were not statistically significant for CBT compared with active controls (another psychological therapy or pharmacotherapy) (OR 1.51; 95% CI 0.77 to 2.96, 6 studies) or usual care (OR 0.53; 95% CI 0.23 to 1.25, 2 studies). Long-term remission was more likely for CBT compared with active therapy (OR 2.03; 95% CI 1.22 to 3.36; 2 studies), but not compared with waitlist controls (OR 3.22; 95% CI 0.96 to 10.75; 3 studies).

The standard mean difference (SMD) score on standardized scales was used to measure changes in anxiety symptoms. Symptoms were significantly reduced for CBT versus waitlist controls (SMD 0.98; 95% CI -1.21 to -0.74; p<0.00001; I^2=75%; 30 studies), but not compared with active controls (SMD -0.50; 95% CI -1.09 to 0.09; p=0.1; I^2=86%, 8 studies) or usual care (SMD -0.21; 95% CI -0.77 to 0.36; p=0.47; I^2=46%; 3 studies). Long-term remission was similar for CBT compared with waitlist controls (SMD -1.55; 95% CI -3.22 to 0.11; p=0.07, I^2=94%; 4 studies) and active controls (SMD -0.92; 95% CI -2.12 to 0.29; p=0.14; I^2=96%; 4 studies).

Table 7. Systematic Reviews of Cognitive Behavior Therapy

Systematic review	Intervention and Comparison	Measure	Outcome	Number of studies	Summary of Main Findings (95 % CI)
Adolescents 4-19 years old (James, 2015)	CBT versus wait list control	Self-reported measures (see text)	Remission for all anxiety disorders	25	OR = 7.85 (5.31 to 11.60)
			Reduction in anxiety symptoms for all anxiety disorders	30	SMD = -0.98 (-1.21 to -0.74)
Adults (Hunot, 2010)	All types of psychotherapy with components of CBT versus wait list or usual care	Most often a 20% reduction in anxiety symptoms from pre to post intervention (mainly the HAM-A or STAI-T)	Treatment response	8	RR = 0.64 (0.55 to 0.74)
			Reduction in anxiety symptoms	12	SMD = -1.00 (-1.24 to 0.77)
Adults (Mayo-Wilson, 2013)	Media-delivered therapy versus no intervention	Any self-reported measure	Treatment response for GAD	4	RR = 4.60 (2.75 to 7.68)
			Reduction in anxiety symptoms for GAD	10	SMD = 0.95 (0.44 to 1.45)
	Media-delivered therapy versus face-to-face intervention		Treatment response for all anxiety disorders	10	RR = 0.78 (0.56 to 1.09)
			Reduction in anxiety symptoms for all anxiety disorders	24	SMD = -0.23 (-0.36 to -0.09)
Adults (Andrews, 2018)	Internet CBT versus wait list, placebo, or usual care	PSWQ or GAD-7	Treatment of anxiety for GAD	9	Hedge's g effect size = 0.70 (0.39 to 1.01)

Abbreviations: CI=confidence interval; CBT=cognitive behavioral therapy; HAM-A=Hamilton Anxiety Scale; GAD=generalized anxiety disorder; GAD-7=Generalized Anxiety Disorder-7; OR=odds ratio; PSWQ=Penn State Worry Questionnaire; SMD=standard mean difference; STAT-T=Spielberger State-Trait Anxiety Inventory--Trait subscale; RR=risk ratio.

Adults

CBT versus controls or active therapy groups. A Cochrane review of psychological therapies for adults included 25 studies (22 in the meta-analysis) enrolling 1305 participants.[86] Sample sizes ranged from 12 to 119, with an average of 54. Most studies were conducted in the United States and the United Kingdom, with others in Canada and European countries. Most studies were set in out-patient psychiatric or psychology department clinics or community mental health settings, while two were conducted in primary care clinics and one at a university campus. The majority of the participants were female (68.6%) and the mean age across studies was 47.2 years (mean age 38.1 years in studies of adult populations and 61.1 years in studies of elderly populations). Twenty-three studies included participants with a primary diagnosis of generalized anxiety disorder.

Eight studies compared CBT with waitlist control or usual care groups, and one study compared CBT, cognitive therapy, behavioral therapy, and placebo with waitlist controls. Additional studies compared CBT or cognitive therapy with active treatment groups. These included four studies of CBT versus behavioral therapy and/or cognitive therapy; six studies of CBT versus supportive therapy; two studies of CBT versus non-directive therapy in combination with pharmacological treatments; three studies of behavioral therapy versus cognitive therapy; and one study of CT versus analytic therapy.

The Hamilton Anxiety Scale (HAM-A) was the most frequently used clinician-rated outcome measure (13 studies), and the Trait subscale of the Spielberger State-Trait Inventory (STAI-I) was the most frequently used self-report measure (16 studies). Ten studies used the Penn State Worry Questionnaire (PSWQ) in 10 studies, the Beck Anxiety Inventory (BAI) in 9, and the Zung Anxiety Inventory (ZAI) in 8.

In a meta-analysis of studies, clinical response was improved with CBT compared with waitlist or usual care controls (relative risk [RR] 0.64; 95% CI 0.55 to 0.74; 8 studies); CBT compared with psychodynamic therapy (RR 0.77; 95% CI 0.65 to 0.92; 1 study); and cognitive therapy compared with behavioral therapy (RR 0.70; 95% CI 0.56 to 0.87; 5 studies). Results were not significantly different between CBT and supportive therapy (RR 0.86; 95% CI 0.70 to 1.06; 7 studies). At 6 months follow-up, differences were significant for cognitive compared with behavioral therapy 0.70; 95% CI 0.56 to 0.87; 5 studies), but not CBT compared with psychodynamic therapy (RR 0.79; 95% CI 0.62 to 1.01; 1 study) or CBT compared with supportive therapy (RR 0.79; 95% CI 0.59 to 1.06; 3 studies).

The standard mean difference (SMD) score on standardized scales was used to measure changes in anxiety symptoms. Symptoms were significantly reduced with CBT versus waitlist or usual care controls (SMD -1.00; 95% CI -1.24 to -0.77; 12 studies); CBT versus psychodynamic therapy (SMD -6.85; 95% CI -11.20 to -2.50; 2 studies); and CBT versus supportive therapy (SMD -0.40; 95% CI -0.66 to -0.14; 7 studies); but not with CBT versus behavioral therapy (SMD -0.05; 95% CI -0.40 to 0.30; 4 studies). Differences between groups were significant at 6 months follow-up for CBT versus psychodynamic therapy (SMD -13.41; 95% CI -19.09 to -7.74; 2 studies); and CBT versus supportive therapy (SMD -0.42; 95% CI -0.83 to -0.02; 3 studies); but not for cognitive versus behavioral therapy (SMD -0.11; 95% CI -0.59 to 0.37; 2 studies).

Differences were not significant at 12 months follow-up for CBT versus supportive therapy (SMD -0.57 (95% CI -1.24 to 0.10, 1 study) or cognitive versus behavioral therapy (SMD 0.06; 95% CI -0.45 to 0.58; 2 studies).

Media-delivered CBT versus controls or face-to-face CBT. A Cochrane review comparing media-delivered therapy of any type (print, audio or video recordings, or computers, including the internet) with no intervention and with face-to-face CBT or behavioral therapy in adults with anxiety disorders included 101 studies (91 studies in meta-analysis) enrolling 8043 participants.[88] Most participants were white (94%) and female (67%), with a mean age of 37 years. The review included 10 studies of GAD, while the other studies included other anxiety disorders.

In a meta-analysis of studies, clinical response was improved for media-delivered interventions compared with no intervention for all anxiety disorders (RR 2.34; 95% CI 1.81 to 3.03; 21 studies) and for GAD specifically (RR 4.60; 95% CI 2.75 to 7.68; 4 studies). Symptoms were significantly reduced in studies comparing media-delivered interventions with no intervention for all anxiety disorders (RR 0.67; 95% CI 0.55 to 0.78, 76 studies), but not for GAD specifically (RR 0.95; 95% CI 0.44 to 1.45; 10 studies). Recovery as determined by the clinical assessment at post-treatment was reduced for media-delivered interventions compared with no intervention for all anxiety disorders (RR 0.40; 95% CI 0.20 to 0.60; 9 studies).

Symptoms were reduced for media-delivered compared with face-to-face interventions (SMD -0.23; 95% CI -0.36 to -0.09; 24 studies), while clinical response (RR 0.78; 95% CI 0.56 to 1.09; 10 studies) and recovery were not (RR 1.05; 95% CI 0.88 to 1.24; 6 studies).

Internet CBT versus controls or face-to-face CBT. A systematic review comparing internet CBT with face-to-face CBT, a waitlist control, information control, care as usual, or placebo in adults with either depression or anxiety included nine studies of 1103 participants.[85] Among participants treated for GAD, differences in symptoms between internet CBT and all other treatments combined were not significant (Hedge's g effect size 0.70; 95% CI 0.39 to 1.01; p=0.00; I^2=82%).

Pharmacological Therapy

Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) are the first-line pharmacologic therapies for anxiety disorders for adults.[96] Although SSRIs and SNRIs not all are FDA approved for children and adolescents, they are first-line treatments for them as well. Azapirone (buspirone) is sometimes used initially, while tricyclic antidepressants and calcium modulators (pregabalin) are considered second line. Benzodiazepines are not recommended for treatment other than during an acute crisis.

Adolescents

A Cochrane review of SSRIs and SNRIs in children and adolescents included short-term (≤16 weeks) trials.[92] Studies ranged in size from 15 to 322 participants with a mean age of 12 years; more than half were female (52.1%). Most trials were conducted in the United States. In this review, two trials treated patients with GAD and three trials included patients with either GAD, social phobia, or separation anxiety disorder. Medications included fluoxetine, fluvoxamine, sertraline (with or without CBT), and venlafaxine-ER.

Treatment response for GAD was improved for all medications compared with placebo for fluoxetine 10-20 mg/day (RR 1.74; 95% CI 1.04 to 2.89); fluvoxamine 50-300 mg/day (dose based on weight) (RR 2.61; 95% CI 1.74 to 3.90); sertraline 50 mg/day (RR 10.00; 95% CI 1.53 to 65.41); sertraline 25-200 mg/day (with or without CBT) (RR 2.32; 95% CI 1.50 to 3.57); and venlafaxine-ER 37.5-225 mg/day (dose based on weight) (RR 1.44; 95% CI 1.19 to 1.75).

A more recent systematic review and meta-analysis included additional medications and reported several outcomes.[97] Improvement in anxiety based on clinician evaluations was statistically significant for all SSRIs and SNRIs evaluated (**Table 8**).

Table 8. Treatment Effects of Anti-Anxiety Medications versus Placebo for Children and Adolescents[97]

Class	Medication	Dose	Effect on Anxiety (clinician report)* Standard Mean Difference (95% CI)
SSRIs	Citalopram (Celexa)	Not approved	-0.43 (-0.67 to -0.19)
	Paroxetine (Paxil)	Not approved	-0.71 (-1.06 to -0.37)
	Sertraline (Zoloft)	50-200 mg	-0.71 (-0.99 to -0.42; 2 trials)
	Fluoxetine (Prozac)	Not approved	-0.40 (-0.72 to -0.01; 2 trials)
SNRIs	Duloxetine (Cymbalta)	30-120 mg	-0.43 (-0.67 to -0.19)
	Venlafaxine (Effexor)	Not approved	-0.42 (-0.74 to -0.10)
	Atomoxetine (Strattera)	Not approved	-0.56 (-0.78 to -0.34; 2 trials)
	Fluvoxamine (Luvox)	Not approved	-0.97 (-1.31 to -0.63; 2 trials)

Abbreviations: CI=confidence interval; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.
*Compared with pill placebo

Adults

The efficacy of SSRIs and SNRIs for treating anxiety in adults has been well established in RCTs and they are generally FDA approved for this use. Information on elderly patients is limited and pregnant women were not included in trials, although these medications are widely used in these patient groups.

A systematic review and network meta-analysis published in 2019 included trials of anti-anxiety medications compared with pill placebo.[98] Treatment effects were measured using scores from the Hamilton Anxiety Rating Scale (HAM-A). Results of for first-line (SSRI, SNRI, buspirone) and second-line (tricyclic antidepressants, calcium modulators) pharmacologic therapies used in the United States are summarized in **Table 9** below. Medications with statistically significant reductions in mean anxiety scores compared with placebo included SSRIs (46 trials; 4,229 participants), SNRIs (22 trials; 3,652 participants), buspirone (6 trials; 311 participants), and pregabalin (11 trials; 1,957 participants).

Table 9. Treatment Effects of Anti-Anxiety Medications versus Placebo for Adults[98]

Class	Medication	Number of Trials; Number of Participants	Difference in Anxiety Score (HAM-A); Mean Difference (95% CrI)	Acceptability (discontinuation); Odds Ratio (95% CrI)
SSRIs	Citalopram (Celexa)	2; 37	-2.22 (-4.28 to -0.19)	3.62 (0.74 to 20.27)
	Escitalopram (Cipralex)	13; 1581	-2.45 (-3.27 to -1.63)	0.96 (0.79 to 1.16)
	Fluoxetine (Prozac)	8; 264	-2.43 (-3.74 to -1.16)	1.36 (0.57 to 3.15)
	Paroxetine (Paxil)	17; 1862	-2.29 (-3.11 to -1.47)	1.24 (1.03 to 1.50)
	Sertraline (Zoloft)	6; 485	-2.88 (-4.17 to -1.59)	0.94 (0.65 to 1.35)
SNRIs	Duloxetine (Cymbalta)	8; 1355	-3.13 (-4.13 to -2.13)	1.09 (0.89 to 1.32)
	Venlafaxine (Effexor)	14; 2275	-2.69 (-3.50 to -1.89)	0.98 (0.83 to 1.16)
Others	Buspirone	6; 311	-2.37 (-3.83 to -0.91)	0.76 (0.47 to 1.25)
	Imipramine (Tofranil)	1; 26	-0.59 (-3.85 to 2.70)	2.83 (0.74 to 12.10)
	Pregabalin (Lyrica)	11; 1957	-2.79 (-3.69 to -1.91)	0.80 (0.66 to 0.98)

Abbreviations: CrI=credible interval; HAM-A=Hamilton Anxiety Rating Scale; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

Contextual Question 2. Adverse Effects of Treatments for Anxiety

Psychological Therapy

In the Cochrane review of 25 studies of psychological therapies for adults, attrition for any reason at post-treatment did not differ between CBT and waitlist or usual care controls (RR 1.00; 95% CI 0.65 to 1.54; 13 studies); or between CBT and various active treatment groups.[86] In a Cochrane review comparing media-delivered therapy with no intervention and with face-to-face CBT, attrition was lower for media-delivered interventions compared with no intervention (RR 0.96; 95% CI 0.94 to 0.99; 78 studies); but not for media-delivered versus face-to-face interventions (RR 0.99; 95% CI 0.95 to 1.03; 28 studies[88]). No other harms were reported.

Pharmacological Therapy

Adverse effects of first line pharmacologic therapies for anxiety are summarized in **Table 10**.

Table 10. Adverse Effects of Anti-Anxiety Medications

Class	Generic	Suggested Daily Dosage			Adverse effects
		Adults	Peds	Elderly	
SSRIs	Citalopram* (Celexa)	20-40 mg	Not approved	≤20 mg	Jitteriness, nausea, restlessness, headache, fatigue, increased or decreased appetite, weight gain, weight loss, tremor, sweating, QTC prolongation, sexual dysfunction, diarrhea, constipation, and other effects.
	Escitalopram (Lexapro)	10 mg	Not approved	10 mg	
	Paroxetine (Paxil)	20-50 mg	Not approved	10-40 mg	
	Sertraline† (Zoloft)	50-200 mg	50-200 mg	50-200 mg	

Class	Generic	Suggested Daily Dosage			Adverse effects
		Adults	Peds	Elderly	
SNRIs	Duloxetine (Cymbalta)	60-120 mg	30-120 mg	30-120 mg	Jitteriness, nausea, restlessness, headache, fatigue, increased or decreased appetite, weight gain, weight loss, tremor, sweating, sexual dysfunction, diarrhea, constipation, urination problems, and other effects.
	Venlafaxine (Effexor)	37.5-225 mg	Not approved	37.5-225 mg	
Azapirone	Buspirone (Buspar)	15-60 mg	Not approved	15-60 mg	Dizziness, nausea, headache, nervousness, lightheadedness, excitement, insomnia, and other effects.

Abbreviations: SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.
*Off-label use

Adolescents

In a Cochrane review of SSRIs and SNRIs in children and adolescents, drop outs due to adverse effects did not differ between treatment and placebo groups for fluoxetine, fluvoxamine, sertraline with CBT, and venlafaxine-ER.[92] The most frequent treatment-emergent adverse effects were abdominal pain and nausea for fluoxetine; abdominal discomfort, increased motor activity, vomiting, tiredness/fatigue, muscle/joint pain, and decreased appetite for fluvoxamine; and anorexia for sertraline without CBT. None were reported for sertraline with CBT.

A more recent systematic review and meta-analysis of trials in children and adolescents included additional medications.[97] The review concluded that SSRIs and SNRIs were associated with increased risk of various short-term adverse effects that were overall not serious, similar to the Cochrane review. Studies were too small or too short to assess the effect on suicidal behavior, although one study found that venlafaxine was associated with a statistically nonsignificant increase in the risk of suicidal ideation.

Adults

A systematic review and network meta-analysis published in 2019 included trials of anti-anxiety medications compared with placebo that reported discontinuation for any reason as an adverse effect.[98] Results indicated no differences in discontinuation between treatment and pill placebo groups (**Table 9 above**). In another systematic review of adverse effects of SSRIs and SNRIs for treating depression (not anxiety) in adults, 63% of patients experienced at least one adverse event, with diarrhea, dizziness, dry mouth, fatigue, headache, nausea, sexual dysfunction, sweating, tremor, and weight gain most commonly reported.[99] In general, trials were too small or too short to assess more serious adverse events, such as suicide, cardiovascular events, or others. Elderly patients were not specifically studied and pregnant women were not included in these trials.

CONCLUSIONS

A summary of evidence is described in **Table 11.** Results of this systematic review of screening for anxiety in women and adolescent girls indicate that no studies have evaluated the overall effectiveness or harms of screening. Thirty studies and two systematic reviews that included 171 studies evaluated the diagnostic accuracy of 27 screening methods and their variations against a clinical diagnosis of generalized anxiety disorder. Screening methods were similar across studies and included predominantly brief clinician or self-administered questionnaires describing symptoms that were easily scored and interpreted. Most studies enrolled predominantly women in community or primary care settings that are highly applicable to population screening and used DSM criteria as the reference standard.

Overall, most screening methods demonstrated moderate to high discriminatory accuracy in studies. For adolescents, studies of four versions of SCARED indicated sensitivity ranging from 64% to 74% and specificity from 64% to 73%. Notably, the 5-item version of SCARED performed similarly to longer versions. Other methods for adolescents demonstrated varying accuracy, with the highest accuracy reported for the MASC (0.82 AUC specifically for girls).

In adults, results of studies evaluating 10 screening instruments and their variations indicated generally high discriminatory accuracy. Eight studies of the GAD (GAD-2, GAD-7, GAD-Q-IV) were evaluated in large primary care populations and indicated sensitivity ranging from 70% to 97% and specificity from 50% to 89%; AUCs from 0.77 to 0.94; with most results falling in the high end of these ranges. The GAD-2, with only two questions performed as well as longer versions. Results were similar for the other methods studied, even when the method involved asking only one question.

For pregnant and postpartum women, results of studies of the EPDS, commonly used for depression screening, indicated varying results for anxiety. Compared to DSM criteria, sensitivity of the EPDS ranged from 70% to 89% and specificity from 27% to 82%, with AUC 0.62. Accuracy was lower with a brief version of the EPDS that emphasized the anxiety subscale. Additional methods for general populations (BAI, GAD-7, GHQ, STAI) were more accurate than methods specific to pregnancy and postpartum (PRT, PRAQ-R, McDonald Prenatal Screening Tool). Use of the EPDS for screening in practice would be an efficient method for both anxiety and depression in pregnant and postpartum women in clinical settings, although pairing the EPDS with the GAD-7 would also be feasible.

For older adults, methods specific to older patients (ADS, FEAR) had similar diagnostic accuracy as the HADS and GAD-7, while the BSI-18 was less accurate.

Studies of treatment for anxiety indicate that CBT is effective in reducing symptoms and improving remission in adults and adolescents. SSRIs and SNRIs are the most common first-line pharmacologic treatments that have proven efficacy in RCTs. Combination therapy of CBT and anti-anxiety medication is often more effective than monotherapy, although CBT may be preferred for pregnant women and those not tolerating anti-anxiety medications.

In conclusion, studies support a strong evidence base of moderate to highly accurate methods of screening for anxiety that are applicable to clinical practices serving women and adolescent girls in the United States. Brief instruments with as few as two questions are as accurate as longer instruments and are particularly useful for routine screening in primary care settings. Once identified, women with anxiety may benefit from CBT with or without pharmacologic therapies depending on severity of symptoms and preferences. CBT and anti-anxiety medications have proven effectiveness in randomized trials. The SSRIs and SNRIs are widely used and generally well-tolerated. These therapies are also effective for depression, which often accompanies anxiety or can develop subsequently.

Table 11. Summary of Evidence

Key Questions			
Question	**Studies; N**	**Summary of Findings**	**SOE; applicability**
KQ 1. Effectiveness of screening for anxiety	No studies	Not applicable	Insufficient
KQ 2. Accuracy of screening methods	30 studies and 2 SRs of 27 methods (N>100,000)	Methods have moderate to good discriminatory accuracy in identifying anxiety in primary care and maternity populations	High; moderate
KQ 3. Harms of screening	No studies	Not applicable	Insufficient
Contextual Questions			
Question	**Summary of Findings**		
CQ 1. Effectiveness of treatment for anxiety—CBT	Trials of CBT versus waitlist or usual care indicate improved remission/clinical response and reduced symptoms for various types of CBT		
CQ 1. Effectiveness of treatment for anxiety—medication	SSRIs and SNRIs are recommended as first-line medication treatment for anxiety based on efficacy RCTs. FDA approval for pediatric and pregnant populations is limited and some are used off label. Additional medications are effective for specific anxiety disorders or when SSRI/SNRIs are not effective or tolerated.		
CQ 2. Harms of treatment for anxiety—CBT	No studies reported harms of CBT.		
CQ 2. Harms of treatment for anxiety—medication	SSRIs and SNRIs are widely used and well-tolerated although adverse effects have been described and vary by medication. Discontinuation rates are similar between medications and pill placebos in trials.		

Abbreviations: CBT=cognitive behavioral therapy; CQ=contextual question; FDA=Food and Drug Administration; KQ=key question; RCT=randomized controlled trial; SNRI=serotonin-norepinephrine reuptake inhibitor; SR=systematic review; SSRI=selective serotonin reuptake inhibitor.

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APPENDIX 1

ICD-10 criteria for Generalized Anxiety Disorder

Note: For children different criteria may be applied (see F93.80).

A. A period of at least six months with prominent tension, worry, and feelings of apprehension, about everyday events and problems.
B. At least four symptoms out of the following list of items must be present, of which at least one from items (1) to (4).
   Autonomic arousal symptoms
   (1) Palpitations or pounding heart, or accelerated heart rate.
   (2) Sweating.
   (3) Trembling or shaking.
   (4) Dry mouth (not due to medication or dehydration).
   Symptoms concerning chest and abdomen
   (5) Difficulty breathing.
   (6) Feeling of choking.
   (7) Chest pain or discomfort.
   (8) Nausea or abdominal distress (e.g. churning in the stomach).
   Symptoms concerning brain and mind
   (9) Feeling dizzy, unsteady, faint or light-headed.
   (10) Feelings that objects are unreal (derealization), or that one's self is distant or "not really here" (depersonalization).
   (11) Fear of losing control, going crazy, or passing out.
   (12) Fear of dying.
   General symptoms
   (13) Hot flashes or cold chills.
   (14) Numbness or tingling sensations.
   Symptoms of tension
   (15) Muscle tension or aches and pains.
   (16) Restlessness and inability to relax.
   (17) Feeling keyed up, or on edge, or of mental tension.
   (18) A sensation of a lump in the throat or difficulty with swallowing.
   Other non-specific symptoms
   (19) Exaggerated response to minor surprises or being startled.
   (20) Difficulty in concentrating or mind going blank, because of worrying or anxiety.
   (21) Persistent irritability.
   (22) Difficulty getting to sleep because of worrying.
C. The disorder does not meet the criteria for panic disorder (F41.0), phobic anxiety disorders (F40.-), obsessive-compulsive disorder (F42.-) or hypochondriacal disorder (F45.2).
D. Most commonly used exclusion criteria: not sustained by a physical disorder, such as hyperthyroidism, an organic mental disorder (F0) or psychoactive substance-related disorder (F1), such as excess consumption of amphetamine-like substances, or withdrawal from benzodiazepines.

APPENDIX 2

Search Strategies

Database: Ovid MEDLINE(R)

Search Strategy:

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1 exp ANXIETY/di, dg, ep [Diagnosis, Diagnostic Imaging, Epidemiology] (12932)
2 exp Anxiety Disorders/di, dg, ep [Diagnosis, Diagnostic Imaging, Epidemiology] (26084)
3 1 or 2 (37783)
4 exp Mass Screening/ (114966)
5 3 and 4 (787)
6 (generaliz* adj3 anxi*).mp. (5482)
7 4 and 6 (83)
8 (generaliz* adj3 anxi* adj7 screen*).mp. (61)
9 5 or 7 or 8 (851)
10 limit 9 to female (704)
11 exp Women's Health/ (26041)
12 9 and 11 (6)
13 10 or 12 (704)
14 (screen* adj7 anxi*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1943)
15 (screen* adj7 (women or woman or female*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (29708)
16 3 and 15 (161)
17 11 and 14 (18)
18 limit 14 to female (1540)
19 17 or 18 (1541)
20 13 or 19 (2001)
21 limit 20 to english language (1895)
22 limit 21 to (comparative study or controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews) (358)
23 exp Epidemiologic Studies/ (2123303)
24 21 and 23 (742)
25 24 not 22 (615)
26 21 not (22 or 24) (922)

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
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1 (generaliz* adj3 anxi*).mp. [mp=title, short title, abstract, full text, keywords, caption text] (30)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
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1 (generaliz* adj3 anxi* adj10 (screen* or diagnos* or detect* or identif*) adj15 (woman or women or female*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (63)
2 (generaliz* adj3 anxi* adj10 (tool* or survey* or instrument* or questionnair*) adj15 (woman or women or female)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (29)
3 1 or 2 (87)
4 (generaliz* adj3 anxi* adj10 (tool* or survey* or instrument* or questionnair*)).mp. (105)
5 (generaliz* adj3 anxi* adj10 (screen* or diagnos* or detect* or identif*)).mp. (264)
6 4 or 5 (342)
7 6 not 3 (255)

Database: Health and Psychosocial Instruments
Search Strategy:
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1 (generaliz* adj3 anxi* adj10 (tool* or survey* or instrument* or questionnair*)).mp. [mp=title, acronym, descriptors, measure descriptors, sample descriptors, abstract, source] (17)
2 (generaliz* adj3 anxi* adj10 (screen* or diagnos*)).mp. [mp=title, acronym, descriptors, measure descriptors, sample descriptors, abstract, source] (30)
3 1 or 2 (38)

APPENDIX 3

Inclusion/Exclusion Criteria

	Included	Excluded
Populations	• Adult and adolescent women age 13 and older	• <13 year old women, studies with <50% women in population, animals
Conditions	• Generalized anxiety disorder or anxiety not yet defined	• Specific to PTSD, OCD, panic disorder, anxiety associated with a disease or illness, other mental health condition
Interventions	• Screening instrument or method used in primary care applicable setting to assess anxiety	• Other interventions • Unclear intervention description • Treatment for anxiety (CQ)
Reference standard	• DSM criteria • Other diagnostic criteria, or adaptations of established criteria	• Screening instrument or method of interest used as reference standard • No reference standard • Inadequate description of reference standard used
Outcomes	**KQ 1:** Improvement in symptoms, quality of life and function **KQ 2:** Diagnostic accuracy (sensitivity, specificity, PPV, NPV, AUC) **KQ 3:** False positives, additional anxiety, any potential harms mentioned by the study	• Prevalence, risk factors, cost, cost-effectiveness
Study Design	• Diagnostic accuracy studies • Randomized controlled trials • Prospective cohort studies • Case-control studies • Systematic reviews	• Case reports • Cost effectiveness studies • Modeling studies

Abbreviations: KQ: key question.

APPENDIX 4

Quality Rating Criteria

Diagnostic/Concordance Studies[100]

Criteria:

- Test applied to an appropriate spectrum of patients (with and without disease/condition), avoiding case-control design
- Population tested was consecutive or random
- Clear eligibility criteria described and rigorous assessment of disease/condition
- Attrition reported and minimal loss to follow-up
- Test is adequately described and reproducible
- Test was validated in a second population group
- Test is an available standard case definition
- Diagnostic test is applied to all patients
- Blinding of outcome assessors to the reference standard

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 500) broad-spectrum patients with and without disease; study attempts to enroll a random or consecutive sample of patients who meet inclusion criteria screening cutoffs pre-stated.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (100 to 500 subjects) and a "medium" spectrum of patients (i.e. applicable to many settings where the diagnostic test would be applied).

Poor: Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; small sample size (<100) of very narrow selected spectrum of patients (components of study not well described).

Systematic Reviews[15]

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance (especially important for systematic reviews)

Definition of ratings based on above criteria:

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies

APPENDIX 5

Strength of Evidence

The strength of evidence for each key question is assessed by using the approach described in the AHRQ Methods Guide.[27] Grades are based on:

- Study limitations (low, medium, or high level of study limitations)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)
- Reporting bias (suspected or undetected)

An overall grade of high, moderate, low, or insufficient is assigned according to a four-level scale by evaluating and weighing the combined results of the above domains:

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

Applicability

Applicability (external validity) is estimated by examining the characteristics of the patient populations; the sample size of the studies; clinical settings (e.g., primary care, community setting); and clinical relevance of the screening approach. Variability in the studies may limit the ability to generalize the results to other populations and settings. Applicability is rated high, moderate, or low.