Revista Brasileira de Psiquiatria. 2013;35:S3–S21

doi:10.1590/1516-4446-2013-S108

UPDATE ARTICLE

Pediatric anxiety disorders: from neuroscience to evidence-based clinical practice

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The objective of this narrative review of the literature is to describe the epidemiology, etiology, pathophysiology, diagnosis, and treatment of pediatric anxiety disorders. We aim to guide clinicians in understanding the biology of anxiety disorders and to provide general guidelines for the proper diagnoses and treatment of these conditions early in life. Anxiety disorders are prevalent, associated with a number of negative life outcomes, and currently under-recognized and under-treated. The etiology involves both genes and environmental influences modifying the neural substrate in a complex interplay. Research on pathophysiology is still in its infancy, but some brain regions, such as the amygdala and the prefrontal cortex, have been implicated in fear and anxiety. Current practice is to establish diagnosis based purely on clinical features, derived from clinical interviews with the child, parents, and teachers. Treatment is effective using medication, cognitive behavioral therapy, or a combination of both. An introduction to the neuroscience behind anxiety disorders combined with an evidence-based approach may help clinicians to understand these disorders and treat them properly in childhood.

Keywords: Child; adolescent; anxiety disorders; obsessive-compulsive disorder

Introduction

Pediatric anxiety disorders refer to a collection of syndromes characterized by dysfunctional fear and/or anxiety affecting children and adolescents. Fear can be defined as a negative emotional state triggered by the presence of a stimulus that has the potential to cause immediate harm, while anxiety can be defined as an emotional state in which the threat is not immediately present but is anticipated. Both of these emotions are adaptive and essential for survival. They are accompanied by cognitive representations, physical symptoms, and behavioral modifications that prepare the individual to deal with danger (fear response). Fear and anxiety are considered dysfunctional when intensity, duration, and/or frequency are not proportional to the eliciting threat, and thereby cause interference, disabilities, impairment, and/or distress that are judged clinically excessive.

Anxiety disorders in childhood and adolescence are associated with a variety of negative outcomes, including lower educational achievement and failure to attend university.[1] They affect children's functioning with peers, school personnel, and family,[2,3] are associated with general psychosocial impairment and disabilities[2,3] as well as with childhood suicide risk even when they are present in subthreshold levels.[4] Pediatric anxiety disorders can also persist and continue to create interference as the child matures into early adulthood, especially when associated with depression.[5] Later in life, anxiety disorders are associated with poorer quality of life,[6] suicide,[7] and increased mortality due to cardiovascular diasease,[8] generating a high societal burden and costs.[9] Despite high prevalence and associations with various negative outcomes, childhood anxiety is rarely recognized by parents and children as a medical problem, leading a minority of affected individuals to receive the care they need.[10,11] Furthermore, physicians can fail to recognize pediatric anxiety in children who do present for care, and even when anxiety is recognized, it is frequently treated sub-optimally.[9,12,13]

The objective of this review was to describe the epidemiology, etiology, pathophysiology, diagnosis, and treatment of pediatric anxiety disorders. Given the fact that anxiety disorders more often co-occur and given the amount of similarities among these syndromes, this paper broadly discusses ideas that are relevant to anxiety disorders as a group.[14] Moreover, when considering individual conditions, the review focuses in depth on four specific disorders: separation anxiety (SeAD), social

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anxiety (SoAD), generalized anxiety (GAD), and panic (PD) disorders. Evidence related to specific phobias (SPs), obsessive-compulsive (OCD), and posttraumatic stress (PTSD) disorders, when relevant, is also incorporated though in less detail.

Epidemiology

Prevalence

Anxiety disorders as a group constitute the most common mental health problem in childhood and adolescence,[15] affecting from 2.5 to 30% of youths.[15-18] Large variations in prevalence rates are observed among studies. While the exact reasons for such variations remain unclear, most experts attribute them to methodological factors such as cross-study differences in the age of subjects, assessment instruments, information source, diagnostic system used, or variations in the application of the diagnostic criteria.[19-22] Nevertheless, cross-cultural variability in prevalence rates for anxiety is also likely to occur, given large differences in risk factor profiles and cultural beliefs.[20,21,23] One reasonable estimate for the global prevalence of any anxiety disorder in the age range of 3 to 17 years, adjusted for differences in methodological factors, is 7.2%.[24] There is no nationally representative study for pediatric anxiety in Brazil. The available studies are limited to cities in the South and Southeast, where reported prevalence is approximately 5%.[25,26]

Prevalence for each anxiety disorder is heavily dependent on the age range of the sample and on the age of onset patterns of each disorder. SeAD and SP have the earliest age of onset, with half of the cases emerging before ages 5 and 8, respectively. SoAD and OCD typically emerge at early adolescence, with half of the cases emerging before ages 12 and 14, respectively. GAD is also common in early adolescence and less well studied than the other disorders, due to changes in diagnostic criteria over time. Nevertheless, current data place the median age of onset in late adolescence, by the ages of 16-18 years. Agoraphobia, PD and PTSD are low prevalence conditions in childhood, with higher prevalence rates in late adolescence and early adults (median age of onset 17, 19 and 22, respectively).[15] Beyond data on age trends, anxiety disorders have also been linked to other demographic factors. Gender is probably the most frequent demographic correlate of pediatric anxiety. The female/male gender ratio for almost all anxiety disorder is 2:1 to 3:1.[27] Most studies have shown an association between anxiety and lower instruction levels and worse socioeconomic status[19] but no association has been found with urbanization or ethnicity.[16,19] Table 1 depicts the prevalence found in two Brazilian studies and other two representative samples in the United States and Europe.

Natural course

Prospective studies have shown that 60-80% of adults with full criteria for anxiety disorders report signs of earlier, pediatric anxiety.[29] Despite the fact that most affected adults have signs of anxiety as children, in children followed prospectively, anxiety disorders have variable natural course. This course typically involves one of four trajectories: 1) spontaneous long-term remission (e.g., childhood SeAD that totally disappears in an otherwise typically developing adolescent who matures to become a healthy adult); 2) strict homotypic continuity (e.g., SoAD in childhood persisting into SoAD in adulthood); 3) broad homotypic continuity (e.g., SeAD in childhood predicting PD in adulthood); and 4) sequential heterotypic comorbidity (e.g., SoAD in childhood predicting latter development of major depression in adulthood).[15,19,30,31] The latter two trajectories involve a course that has been characterized as waxing and waning over time,[32] oscillating between threshold and subthreshold clinical conditions (resulting in high rates of recurrence rather than chronicity).[33]

The frequency of each one of these courses is highly variable from one longitudinal study to another.[1,5,29,32,34-42] Broadly we can say that about one-third of anxious children achieve a long-term remission, another third part persists with strict or broad anxiety continuity (frequently accompanied by comorbid disorders), and about one-third remits from anxiety and develops a sequential heterotypic comorbidity (mainly with major depression and substance abuse).[1,29,38,40] Among a variety of potential moderators of the natural history, unfavorable natural courses have been associated with female gender, symptom severity, duration of illness, early age of onset, severe avoidance and associated impairment, parental history of psychopathology, and inhibited temperament.[15,43]

Etiology and pathophysiology

Mental disorders reflect individual differences in brain function.[31,44,45] Those differences are a result of a complex combination of factors that ultimately represent the distal effects of risk genes and/or environmental components (etiological factors). These etiological risk factors act on neural circuits (neural substrates) during brain development and cause quantitative and/or qualitative abnormalities in brain functions (pathophysiological processes). This deviation from typical trajectories of brain development results in emotional and behavioral manifestations of psychiatric disorders.[46]

Genes and environment

Family studies have shown that anxiety disorders are familial,[47,48] whereas twin studies demonstrated that anxiety disorders are heritable[49] and that the proportion of the phenotypic variability explained by genetic factors (heritability) for anxiety disorders ranges from 25-60%.[49-52] In general, this represents modest heritability for a psychiatric condition, clearly meaningful but lower than for highly heritable conditions, such as attention deficit hyperactivity disorder (ADHD) or autism.[53] In addition, one study[54] investigating common childhood psychiatric disorders found that a general set of genes might nonspecifically influence risk for childhood psychiatric disorders,

Table 1 Diagnostic criteria for pediatric anxiety disorders and epidemiology[28]

	Simplified DSM-IV diagnostic criteria	Prevalence (%)		Age of onset
		Children	Adolescents	
Generalized anxiety disorder (GAD)	A - Anxiety and excessive worry, most of the days, about a number of events for at least 6 months. B - Worry is difficult to control. C - At least one of the following: 1) restlessness; 2) easily fatigued; 3) difficulty concentrating or mind going blank; 4) irritability; 5) muscle tension; 6) sleep disturbance.	TAU: 0.4 PEL: 1.4	NCS: 2.2 EDSP: 0.8	EDSP: 19 years
Social anxiety disorder (SoAD)	A - Marked and persistent fear of social or performance situations when exposed to unfamiliar people or potential humiliation/embarrassment (must occur with peers, not just with adults). B - Exposure to the feared social situation provokes anxiety (e.g., crying, tantrums, freezing, or shrinking). D - Social or performance situations are avoided or faced with intense anxiety or distress. F - At least 6 months.	TAU: 0.7 PEL: 0.1	NCS: 9.1 EDSP: 3.5	EDSP: 12.5 years
Separation anxiety disorders (SeAD)	A - Excessive anxiety when away from home or from attachment figures or when separation is anticipated, with at least three of the following: 1) distress; 2) worry about losing or harm befalling attachment figures; 3) worry that an untoward event will lead to separation; 4) reluctance/refusal to go to school or elsewhere; 5) fearful/reluctant to be alone or without attachment figures; 6) reluctance/refusal to go to sleep without an attachment figure or to sleep away from home; 7) nightmares with separation; 8) physical symptoms. B - At least 4 weeks.	TAU: 1.4 PEL: 0.7	NCS: 7.6	EDSP: 4.5 years
Panic disorder (PD)	A - Recurrent unexpected panic attacks (i.e., intense anxiety of sudden onset and brief duration), with at least one of them followed by at least 1 month of at least one of the following: 1) concern about additional attacks; 2) worry about the implications/consequences of the attack; 3) significant change in behavior related to the attacks. B - Presence or absence of agoraphobia (differential diagnosis for PD with or without agoraphobia).	TAU: 0.0 PEL: 0.0	NCS: 2.3 EDSP: 1.6	EDSP: 18.5 years
Specific phobias (SP)	A - Marked and persistent excessive or unreasonable fear cued by the presence or anticipation of a specific object or situation (e.g., flying, heights, animals, injection, blood). B - Exposure to the phobic stimulus provokes anxiety (e.g., crying, tantrums, freezing, or clinging). D - Phobic situation(s) is(are) avoided or faced with intense anxiety or distress; F - At least 6 months.	TAU: 1.0 PEL: 1.4	NCS: 19.3 EDSP: 2.3	EDSP: 7 years
Obsessive-compulsive disorder (OCD)	A - Either obsessions (i.e., repetitive intrusive/inappropriate thoughts, impulses, or attempts to ignore, suppress, or neutralize them with other thoughts or actions) or compulsions (i.e., repetitive behaviors or mental acts, or according to rules, and to reduce distress or prevent event). C - Obsessions/compulsions cause marked distress and are time consuming ($>$ 1 hour a day).	TAU: 0.1 PEL: 0.1	EDSP: 0.7	EDSP: 14.5 years
Posttraumatic stress disorder (PTSD)	A - Past exposure to a traumatic event responding with intense fear, helplessness, horror, or disorganized or agitated behavior. B - Re-experience of the traumatic event through at least one of the following: 1) intrusive recollections of the event or repetitive play of the trauma; 2) dreams of the event or frightening dreams; 3) feeling as if the traumatic event were recurring; 4 and 5) intense psychological distress or physiological reactivity at exposure to internal or external cues that resemble an aspect of the traumatic event. C - Avoidance of stimuli associated with the trauma and numbing of general responsiveness, with at least three of the following (not present before the trauma): 1) efforts to avoid thoughts, feelings, or conversations related to the trauma; 2) efforts to avoid activities, places, or people that arouse recollections of the trauma; 3) inability to recall aspects of the trauma; 4) markedly diminished interest or participation in significant activities; 5) feeling of detachment from others; 6) restricted range of affect; 7) sense of a foreshortened future. D - Increased arousal (not present before the trauma), with at least two of the following: 1) difficulty falling or staying asleep; 2) irritability or outbursts of anger; 3) difficulty concentrating; 4) hypervigilance; 5) exaggerated startle response. E - More than 1 month.	TAU: 0.1 PEL: 0.1	NCS: 5.0 EDSP: 1.3	EDSP: 22.5 years

Diagnostic criteria for all anxiety disorders: the focus of the anxiety symptoms is not confined to features of another mental disorder. The anxiety symptoms cause clinically significant distress or impairment in social, family, school, or other important areas of functioning. The disturbance is not due to the effects of a substance, general medical condition, or another mental disorder. EDSP = Early Developmental Stages of Psychopathology (Composite - International- Diagnostic Interview - CIDI, lifetime, ages 14-24); GSM = Great Smoky Mountains Study (Child and Adolescent Psychiatric Assessment - CAPA, 3-month prevalence, ages 9-16); NCS = National Comorbidity Survey - Adolescent (CIDI, lifetime, ages 13-18); PEL = Pelotas Study (Development and Well-Being Assessment - DAWBA, current, ages 11-12); TAU = Taubaté Study (DAWBA, current, ages 7-14).

whereas two additional sets of genes might influence risk for two more narrow aspects of illness, reflecting still broad risks for internalizing and externalizing disorders, respectively. Environmental factors generally involve non-shared environment effects; meaning factors that tend to make individuals within a family appear different. Such factors include aspects of an individual child's school environment, the unique stressors he or she experiences, and their social situation. This is somewhat consistent with the generalist genes, specialist environment model, i.e., that common psychopathology mostly share their genetic liability, but are differentiated by non-shared experiences.

Twin studies that specifically focused on pediatric anxiety also support the role of both genes and environment, but the role of the shared environment also appears to be significant with lower genetic effects. These types of studies focus more narrowly on specific presentations of anxiety, in contrast to studies more broadly examining varieties of psychopathology. These more narrow studies are incapable of specifying what genes and environmental factors are particularly noteworthy for pediatric anxiety. Nevertheless, no twin study is capable of clarifying how any set of genes and environments affects the brain unless the study directly assesses brain function. It is only through effects on the brain that genes and the environment can ultimately result in emotional and behavioral abnormalities.[48] Candidate gene studies search for specific loci at the genome. While these have been criticized as being vulnerable to type I errors, they have identified several risk genes for anxiety disorders[55]; however, consistent with type I errors, a recent review suggested that available work resulted in "not a single instance of replication."[56] Genome-wide association studies (GWAS) search the entire genome for signs of association. When performed properly, these are less vulnerable to type I errors. To date, five such GWAS have been performed on anxiety disorders,[57-62] though none of these focuses on children. Among the five, two of them produced significant results. Otowa et al.[59] found two genes that achieved genome-wide significance (transmembrane protein 16B and plakophilin 1), but a subsequent study failed to replicate these findings in PD patients.[58,63] In another study, a variant in the retinoid-related orphan receptor alpha gene (RORA) showed genome-wide significance for PTSD.[61] In addition to these five GWAS investigations, other studies have investigated the excess of rare copy number variations (CNVs), which are relative large segments of DNA that are either deleted or duplicated. In this area, the only study on PD failed to find genome-wide significance.[64]

While each of these genetic strategies has advantages, they also are relatively insensitive to many mechanisms. For example, available evidence finds signs of complex gene-environment interplay in anxiety disorders,[65-69] and most research on genetics is poorly suited for capturing such effects. Genes and environments shape anxiety and other behaviors through a complex interplay, as it has been shown through three specific relationships: 1) gene-environment interaction (genetically influenced sensitivity to specific environments); 2) gene-environment correlation (genetic influences on individual variation in people's exposure to particular environments); 3) epigenetics (environmental moderation of the effects of genes through influences in gene expression).[70] As understanding of genes and the environment accrue, the complexity of these three sets of relationships is likely to appear even greater. This suggests that, for anxiety and other so-called complex behaviors influenced by multiple factors, the effects of genes are far from deterministic and cannot be dissociated from the effects of the child's environmental conditions. Figure 1 illustrates these complex relationships.

Pathophysiological processes and neural substrate

Despite a considerable advance over the last years, little is known about the neural underpinnings of anxiety disorders in children and adolescents. Most of the work in this area focuses on information processing functions involved in emotional processing (in particular threat processing) and cognitive control.[31,71]

The state of knowledge about mental processes involved in pediatric anxiety is currently limited. Nevertheless, tentative conclusions about existing relationships can be drawn. In particular, a set of dysfunctional mental processes has been linked to pediatric anxiety and associated traits, such as the early-childhood temperament of behavioral inhibition. These dysfunctional processes can be classified into five groups of information-processing functions: 1) threat-attention interaction (a tendency for anxious children to automatically orient their attention towards or away from threats)[72]; 2) threat appraisal (a tendency for anxious children to classify and respond to neutral or harmless stimuli as if they are dangerous)[73]; 3) memory and learning processes (a tendency for anxious individuals to learn different associations among safe and dangerous stimuli, as presented in fear conditioning and extinction experiments)[73-75]; 4) social evaluative processes (a tendency for anxious children to become concerned about peer evaluation)[76]; 5) increased sensitivity to rewards (a tendency for anxiety children to more strongly alter their behavior when trying to achieve rewards).[77,78]

This set of findings suggests that anxiety disorders involve dysfunctional processes in various emotional and cognitive processes, each of which is in turn regulated by several brain regions that may support anxiety disorder pathophysiology.[31,71] Some of the regions include: the amygdala, several portions of the prefrontal cortex - particularly the ventrolateral and dorsomedial divisions - and dysfunctions in the basal ganglia, particularly in patients with OCD.[31,71,79,80]

Parenting, life events, and modeling/learning

Several studies have linked various environmental factors to risk for anxiety. These factors include features of the home, such as overprotective/over-controlling parenting

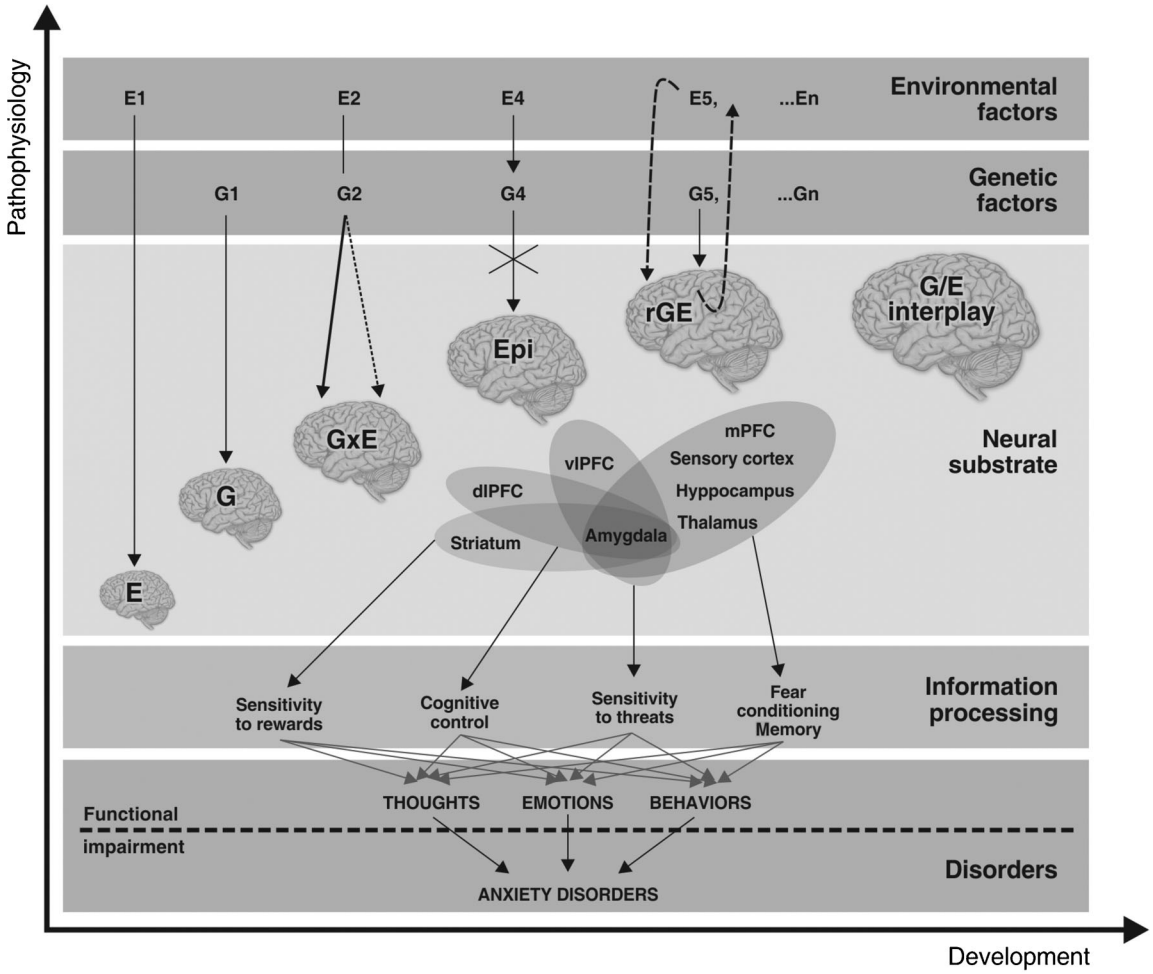

Figure 1 Schematic representation of the etiological and pathophysiological process related to anxiety disorders. E1, main environmental effects (E); G1, main genetic effects (G); E2xG2, example of gene environment interaction (GxE; genetic sensitivity to specific environments); E4→G4, example of epigenetic regulation (Epi; environmental regulation of gene expression); E5↔G5, example of gene environment correlation (rGE; genetic influences on individual variation in people's exposure to particular environments). Genes and environments influence the developing brain. Dysfunctional circuits in the neural substrate result in deficient information processing that ultimately affect individuals' thoughts, emotions, and/or behaviors. Extreme dysfunctions in such system produce functional impairment and are interpreted as anxiety disorders.

style,[81,82] as well as features that can occur either within or outside of the home, such as stressful life events.[83,84] Nevertheless, the evidence so far is limited regarding the direction of these associations. For example, one could hypothesize that some parents who are themselves already anxious might also respond to their child's anxiety or other signs of vulnerability with parenting practices that may further reinforce the child's difficulties, such as failure to encourage infant social responsiveness.[17,85] In other words, such environmental factors could either predispose to anxiety in children or children who are at risk for anxiety may behave in such a way that these environmental factors are preferentially elicited. Kender & Baker found that stressful life events, parenting, family, environment, social support, peer interactions, and marital quality are significantly influenced by genetic factors with heritability estimates ranging from 0.07 to 0.39[68] - suggesting that associations between anxiety and parenting or other environmental factors may be genetically mediated. Other studies found that the effect of parenting was only partially genetically mediated with an important role of non-shared environment.[86] In addition, some authors suggest that some fears may arise as a result of modeling and vicarious learning (i.e., learning through observation of a parent fearful response in a threatening situation for her/him)[87-89] and verbal transmission of threat information about novel objects.[90,91] However, more experimental studies are needed to better understand these phenomena.

Research on influences of parenting in psychiatric disorder illustrates that risk and causality in psychiatry are extremely complex phenomena.[68,69,92-96] In addition, heterogeneity within anxiety disorders is an important factor to consider. Two individuals with similar clinical manifestations may have different dysfunctional processes, and the same dysfunctional process may be

responsible for different clinical manifestations. New initiatives, such as the Research Domain Criteria (RDoC),[97,98] are attempting to clarify the ways in which underlying neural substrates of mental disorders contribute to dimensional traits that are expressed in specific behaviors and that cut across current operationalization of psychopathology.

Dimensional aspects of anxiety

As noted above, fear and anxiety are adaptive responses to potential threats. The expression of these symptoms can range from normative to pathological behavior according to the frequency, intensity, duration and/or interference in functioning. Therefore, anxiety disorders may lie at the extreme end of a continuum, rather than involve symptoms that are exclusive to pathological conditions. As such, anxiety disorders would represent a variation in degree but not in kind.[99] This would imply a view of normal and pathological anxiety as falling along a dimension, with diagnostic thresholds reflecting clinical and societal burden rather than discontinuous pathophysiological states. If this view of anxiety is correct, it would be quite important to study the normal development of fears and learn to recognize temperaments that are closely related to psychopathology in infants. Two such factors associated with anxiety are behavioral inhibition and anxiety sensitivity.

Normal development of fears

Because the development of fear circuitry occurs early, fear responses can be observed very early in life. There are changes in the context of normative fear over the course of development, typically from immediate and concrete stimuli during infancy to anticipatory, abstract, and more global stimuli that characterize adolescent fears. During infancy and toddlerhood, most infants develop a fear of loss and shyness to strangers that peaks around 8 to 12 months of age, as is expressed by wariness around unfamiliar people.[100,101] These fears are often followed by separation anxiety that peaks around 10 to 18 months marked by distress about being separated from parents. For most children, those fears disappear around 2 to 3 years of age. Early childhood (pre-school age) is characterized by normative fears related to specific threats, such as meteors, clouds, blood, end of the world, being kidnapped, fairies, loss of orientation, and dying or death of others. School age is marked by similar fears, including those directed towards wind, darkness, water, domestic animals, insects, ghosts, death, and disease, germs, natural disasters, traumatic events, harm to self or others, school anxiety, and performance anxiety. Adolescence is characterized by fear of negative evaluation and fear of rejection from peers. All normative fears typically decrease with age and are transient. In adolescence, stability begins to become apparent. Increases in prevalence of phobic and anxiety disorders parallel decreases in normative fears.[71]

Behavioral inhibition and anxiety sensitivity

Given the dimensional and developmental nature of internalizing psychopathology, researchers have considered whether certain types of temperaments observed very early in life predict later risk for pediatric anxiety.[102] Most of this work has focused on infants who display heightened reactions to novelty and heightened sensitivity to stimulus variations. Some such infants mature to become toddlers who withdraw from novel or unfamiliar social situations. This group of toddlers is said to manifest the temperament of behavioral inhibition. This temperament places the child at risk for SoAD.[103,104] A recent meta-analysis showed that behavioral inhibition was associated with a seven-fold increased risk for developing SoAD. Given that 15% of infants are classified as behaviorally inhibited and about half of them will develop social anxiety this is one of the most consistent risk factors for social anxiety.[103] Anxiety sensitivity is another dimensionally distributed trait that, like behavioral inhibition, has been linked to pediatric anxiety. Anxiety sensitivity involves beliefs that anxious symptoms will have harmful physical, psychological, or social consequences to the individual. Some studies suggest that this trait predicts PD more specifically than other forms of anxiety, expressed later in life.[105,106] Although these dimensional traits are often seen as risk factors, an alternative conceptualization is that they represent alternative manifestations of overt anxiety disorders, as they are expressed in younger children.

Clinical manifestations and diagnosis

Despite the dimensional perspective of fear and anxiety, diagnostic and clinical decisions (e.g., to treat or not to treat) are categorical and require a classificatory system. According to the DSM-IV, most of the anxiety disorders have the same diagnostic criteria for children, adolescents or adults, with some minor variations in presentation (Table 1).

Screening

Some researchers argue that screening for anxiety disorder should be universal (applied to every child irrespective of their symptoms). Despite that, from a public health perspective, only targeted screening may be possible, and it is not clear whether universal screening would be in the best interest of patients. Therefore, screening may be most helpful among children who present with complaints about excessive fears, extreme shyness, frequent worries or rituals - some kind of emotional distress.

Diagnostic procedures and differential diagnosis

The diagnosis of pediatric anxiety disorder is based on clinical evaluations. First, normal fears should be differentiated from pathological fears. The best way of doing this is evaluating whether fears are: 1) developmentally

expected or not; 2) appear with intensity, duration, and frequency that is higher than expected for the same age; and 3) whether the fears result in distress and impairment.

Second, pathological fears should not be better explained by co-occurring symptoms of another psychiatric disorder, by a co-occurring medical disease, or due to the influences of use/abuse of alcohol and/or other psychoactive substances (as well as not due to withdrawal). Therefore, it is crucial to investigate the situations and context in which the anxiety symptoms manifest.

Third, primary anxiety should be classified according to the type of anxiety disorder. Anxiety disorders share in common several clinical features, namely dysfunctional cognitions, physical symptoms, and behavioral dysfunctions such as avoidance - one of the core symptomatic characteristics of all anxiety disorders. However narrowly defined in diagnostic manuals, specific anxiety disorders also exhibit a substantial degree of phenotypic heterogeneity. Each anxiety disorder has a symptomatic signature. For treatment purposes, it is useful to determine the main anxiety disorder as the condition that produces the greatest distress, impairment, and interference in the child's life. Figure 2 describes the core symptomatic features of the main pediatric anxiety disorders.

Comorbidity

Pediatric anxiety disorders and other childhood psychiatric conditions frequently co-exist in the same patient, a phenomenon known as comorbidity. In clinically referred samples, comorbidity is often the rule rather than the exception,[108] with more than half of the patients having more than one anxiety disorder. In community samples, anxiety also increases the chance of having additional psychiatric diagnoses such as major depression (odds ratio [OR] = 8.2; 95%CI 5.8-12), ADHD (OR = 3.0; 95%CI 2.1-4.3), and oppositional defiant disorder/conduct disorder (OR = 3.1; 95%CI 2.2-4.6).[109] Anxiety disorders and substance abuse and dependence in childhood appear not to be related, but this comorbidity increase dramatically in adolescents and adults, notably in subjects with social anxiety.[110] Therefore a search for comorbidity is imperative when evaluating children with anxiety. This includes a specific search for symptoms of major depression (including suicidal ideation), substance abuse and dependence, ADHD, and oppositional defiant disorder. Two other conditions that are not necessarily disorders but are rather specific behaviors also frequently present in anxious children. These conditions are selective mutism, which is the failure to speak in specific setting despite full use of language at home, and school refusal, which is the failure to attend to school.

The high degree of comorbidity between anxiety disorders, as a group, and depression is clearly notable. In terms of associations between depression and one or another specific anxiety disorder, evidence is mixed in terms of whether associations are particularly strong with specific conditions. Some studies showed particularly strong associations with GAD, potentially reflecting a singular higher order structure for the two conditons.[111] Other findings appear less specific and more strongly reflecting developmental variations.[38]

Assessment

A proper assessment of psychiatric symptoms in childhood involves information derived from the child, parents, and teachers. Particularly for anxiety disorders, the child information is extremely valuable. Since some of the symptoms involve emotions, cognitions, and behaviors that may not involve the parent, it is imperative to consider the child's report. Younger children may have difficulties communicating their symptoms as well as their associated distress and impairments to the physician.[15] In these cases, parental and teacher information may be more valuable, but clinicians still should be vigilant for signs of avoidance expressed by the child. The clinician should be aware that parents often look for help with unexplained physical complaints reflecting heightened arousal (headaches, stomachaches, nausea, vomiting, diarrhea, muscle tension, and difficulty with sleep) that may indicate an underlying pediatric anxiety.[112]

As mentioned above, the diagnosis of any anxiety disorder is clinical. Although several studies link anxiety to various biological or genetic factors, the magnitude of these associations is far too small to be of clinical use when evaluating individual children. Some structured interviews and/or rating scales may be helpful to: 1) screen for anxiety symptoms in non-specialized settings; 2) assess symptom severity; and 3) monitor treatment gains. Table 2 depicts a variety of clinician, self and parent rated instruments that may be useful in research and clinical practice.

Treatment

Both medication and psychotherapy are effective in the treatment of pediatric anxiety symptoms. Literature is reviewed below in four specific areas: 1) non-OCD anxiety disorders (SeAD, SoAD, GAD, and PD); 2) OCD; 3) PTSD; 4) SP.

Because PD is exceptionally rare in childhood and adolescence, insufficient evidence exists from controlled studies to guide treatment.[155] Therefore, clinical management of PD is often considered as an extension of the currently available evidence for more common and better studied anxiety disorders (e.g., SeAD, SoAD and GAD). SPs are also highly comorbid with other anxiety disorders. When isolated, treatment should use cognitive behavioral therapy (CBT), with exposure to the feared object combined with cognitive techniques during the exposure (whether in vivo, imaginary, or virtual) that facilitate extinction. Too few studies examine efficacy of medication in SP to inform recommendations, probably because CBT, the less invasive interventions, is typically effective. Evidence regarding the treatment of PTSD and other consequences of trauma in children most deeply

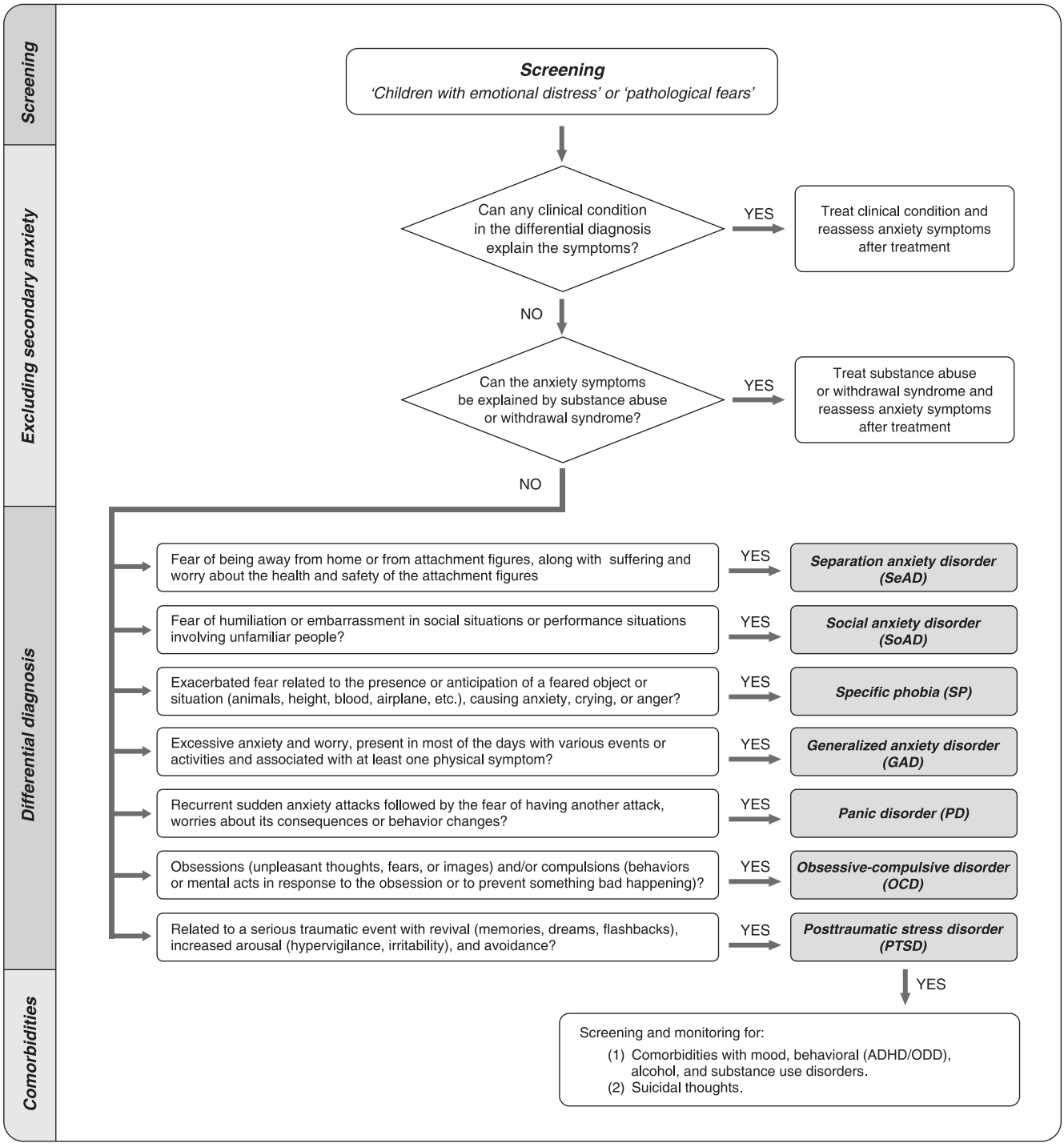

Figure 2 Algorithm for the diagnostic assessment of pediatric anxiety disorders (based on Salum et al.[107]). ADHD = attention deficit hyperactivity disorder; ODD = oppositional defiant disorder

examines CBT, where again, evidence of efficacy is strong.[156] Because the few studies examining medication efficacy in pediatric PTSD are generally equivocal, CBT should be the first-line treatment in children presenting with posttraumatic anxiety.[157] Due to a more specialized characterization of the PTSD treatment, this topic will not be further discussed here. Additional information can be found elsewhere.[157]

Medication + psychoeducation

Placebo-controlled clinical trials demonstrate efficacy for selective serotonin reuptake inhibitors (SSRIs; fluoxetine, fluvoxamine, paroxetine, and sertraline) in both pediatric OCD and non-OCD disorders.[158] Some trials also support the use of serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine for non-OCD disorders.[158]

Table 2 Instruments for the assessment of anxiety symptoms and diagnosis of anxiety disorders in children and adolescents

Clinical instruments for the diagnosis of pediatric anxiety

					Psychometric properties (for anxiety disorders section when available separately)	
Instrument	Rater (informant)	Diagnosis	Estimated time	Diagnostic system	Reliability	Validity
K-SADS* (E/PL)[113-115]	Clinician (C, P, CLIN)	Current/lifetime	--	DSM-IV	TR: 0.80 (current); 0.60 (lifetime) IR: 93%-100% (current); 100% (lifetime); *κ = 0.9 (anxiety)	--
DAWBA*[26,116,117]	Lay/Clinician (C, P, T, CLIN); COMP (C, P, T, CLIN)	Current	30-50 min	DSM-IV; ICD-10	IR: *κ = 0.91 (internalizing)	CONV: 0.13-0.48 (DISC-IV); 0.23-0.48 (CAPA); diagnosed cases probably more severe than DISC-IV and CAPA DISCR: higher rate of diagnosis in a clinic than in a community sample (OR = 13.3)
ChIPS*[118,119]	Clinician (C, P, CLIN)	Current	20-50 min	DSM-IV + Psychosocial stressors	IR: 0.90-1.00	CONV: high levels of agreement with DICA and clinician's diagnosis
DISC-IV[116,120]	Clinician (C, P, CLIN); COMP (C, P, CLIN)	Current	70 min	DSM-IV; ICD-10	TR: 0.48-0.86	CONV: 13-0.48 (DAWBA); 0.21-0.61 (CAPA)
DICA-IV[121,122]	Clinician (C, P, CLIN); COMP (C, P, CLIN)	Current	30-120 min	DSM-IV	--	--
ISCA[123]	Clinician (C, P, CLIN)	Current	45-90 min (C); 120-15 min (P)	DSM-IV	IR: 0.95	--
ADIS-C[124,125]	Clinician (C, P, CLIN)	Current	--	DSM-IV (focus on anxiety disorders)	TR: 0.80 to 0.92 IR: 0.80-1.00	--
CAPA[116,126,127]	Clinician (C, P, CLIN)	Current	60 min	DSM-IV; ICD-10	TR: 0.74-0.79	CONV: 0.23-0.48 (DAWBA); 0.21-0.61 (DISC-IV)
PAPA[128]	Clinician (P, CLIN); COMP (P, CLIN)	Current	100 min	DSM-IV; ICD-10 + RDC-PA; DC: 0-3R	TR: 0.74	--
CIDI-A[16,129]	Lay (C); COMP	Current/lifetime	2.5 hours (C)	DSM-IV; ICD-10	--	CONV: Area Under the Curve > 0.79 (KSADS-PL)

Rating scales for the assessment of anxiety symptoms within a broad anxiety construct

				Psychometric properties		
Scale	Rater	Number of items	Estimated time	Reliability	Validity	Cutoff
STAI-C*[130,131]	Self	20 (state) + 20 (trait)	20 min	--	--	--
RCMAS*[132,133]	Self	37	15 min	IC: 0.83-0.85 *IC: 0.85 *TR: 0.88	--	--
BAI-Y[134]	Self	20	10 min	--	--	--

Rating scales for the assessment of anxiety symptoms of various anxiety dimensions

					Psychometric properties		
Scale	Rater	Items	Estimated time	Dimensions of evaluation	Reliability	Validity	Cutoff
PARS[135,136]	Clinician (C, P, CLIN)	50 + 7-item severity scale	20-30 min	GA; SoA; SeA	IC: 0.64 TR: 0.55 IR: 0.97	CONV: 0.61 (CGI-S) DIVG: 0.18-0.33 (CDRS)	TREAT: 8-10 (84-94% SENS; 82-90% SPEC)

Continued on next page

Table 2 Continued

Rating scales for the assessment of anxiety symptoms of various anxiety dimensions

Scale	Rater	Items	Estimated time	Dimensions of evaluation	Psychometric properties		
					Reliability	Validity	Cutoff
SCARED*[137-140]	Self and parent	41	15 min	GA; PANIC-SOMAT; SeA; SoA; SCHOOL	IC: 0.90 *IC: 0.90 TR: 0.86 *TR: 0.81	*CONV: 0.81 (MASC) *DIVG: 0.58 (CDI) DISCR: anxiety disorders vs. other psychiatric disorders *DISCR: anxiety disorders vs. control	DX: $\geqslant$ 26 (71% SENS; 61-71% SPEC) *DX: $\geqslant$ 23 (81.8% SENS; 52.0% SPEC)
SCAS*[141-143]	Self and parent	38	15 min	GA; PANIC-AG; SeA; SoA; OC; FEARS	IC: 0.92 TR: 0.60	CONV: 0.71 (RCMAS) DIVG: 0.48 (CDI) DISCR: anxiety disorders vs. control	DX: $\geqslant$ 40 boys ages 8-11; $\geqslant$ 33 boys ages 12-15; $\geqslant$ 50 girls ages 9-11; $\geqslant$ 39 girls ages 12-15
MASC[144]	Self and parent	39	15 min	SOMAT; HA; SeA; SoA	IC: 0.90 TR: 0.79-0.93	CONV: 0.63 (RCMAS) DIVG: 0.19 (CDI)	--

Rating scales for the assessment of anxiety symptoms of a specific anxiety dimension

Scale	Rater	Items	Estimated time	Dimension of evaluation	Psychometric properties		
					Reliability	Validity	Cutoff
LSAS-CA[145]	Clinician (C, P, CLIN)	24	--	SoA	IC: 0.95-0.97 TR with IR: 0.94	CONV: 0.75 (SPAI-C) DIVG: 0.38 (CDRS-R) DISCR: social phobia vs. other anxiety disorders and control	DX: $\geqslant$ 23 social phobia vs. control (95.9% SENS; 100% SPEC); $\geqslant$ 30 social phobia vs. other anxiety disorders (91.8% SENS; 65.2% SPEC)
SPAI-C*[146-149]	Self	26	--	SoA	IC: 0.95 / *0.94 TR: 0.63-0.86 / *0.78	DISCR: social phobia vs. control *DISCR: social phobia vs. control	DX: $\geqslant$ 19 (30% FN; 26% FP)
CY-BOCS[150-152]	Clinician (C, P, CLIN), self and parent	81 + 10-item severity scale	--	OC	IC: 0.87-0.90 IR: 0.84 TR: 0.79	CONV: 0.62 (LOI-CV) DIVG: 0.34 (CDI); 0.37 (CMAS)	TREAT: 14 (91% SENS; 90% SPEC)
DYBOCS*[153]	Clinician (C, P, CLIN)	88 + 3 item severity for each OC symptom	40 min	OCD: aggressive, symmetry, contamination, hoarding, miscellaneous	IC: $>$ 0.93 IR: $>$ 0.98	CONV: 0.79 (YBOCS) DIVG: low Pearson coefficients with HAM-A, HAM-D, YGTSS	--
FSSC-R[154]	Self	80	--	FEARS	IC: 0.94-0.95 TR: 0.55-0.82	CONV: 0.46-0.51 (STAI-C) DISCR: school phobia vs. control	--

ADIS-C = Anxiety Disorders Interview Schedule for Children; AG = agoraphobia; BAI-Y = Beck Anxiety Inventory for Youth; C = children as informant; CAPA = Child and Adolescent Psychiatry Assessment; CDI = Children's Depression Inventory; CDRS = Children's Depression Rating Scale; CDRS-R = Children's Depression Rating Scale, Revised; CGI-S = Clinical Global Impression, Severity Scale; ChIPS = Children's Interview for Psychiatric Syndromes; CIDI-A = Composite International Diagnostic Instrument, Adolescent adaptation; CLIN = final clinician impression; CY-BOCS = Children Yale-Brown Obsessive-Compulsive Scale; COMP = computer-assisted; CONV = convergent; DAWBA = Development and Wellbeing Assessment; DICA = Diagnostic Interview for Children and Adolescents; DISC-IV = Diagnostic Interview Schedule for Children, Fourth Edition; DISCR = discriminant; DIVG = divergent; DX = criteria to the diagnosis of pediatric anxiety disorders; DYBOCS = Dimensional Yale-Brown Obsessive-Compulsive Scale; FEARS = specific phobias; FSSC-R = Fear Survey Schedule for Children, Revised; GA = generalized anxiety; FN = false negatives; FP = false positives; HA = harm avoidance; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; IC = internal consistency; IR = interrater; ISCA = Interview Schedule for Children and Adolescents; K-SADS-E = Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version; LOI-CV = The Leyton Obsessional Inventory, Child Version Survey Form; LSAS-CA = Liebowitz Social Anxiety Scale for Children and Adolescents; MASC = Multidimensional Anxiety Scale for Children; OC = obsessions-compulsions; OCD = obsessive-compulsive disorder; P = parent as informant; PAPA = Pre-School Age Psychiatric Assessment; PANIC = panic attacks; PARS = Pediatric Anxiety Rating Scale; RCMAS = Revised-Children's Manifest Anxiety Scale; RDC-PA = Research Diagnostic Criteria, Preschool Age; SCARED = Screen for Child Anxiety Related Emotional Disorders; SCAS = Spence Children's Anxiety Scale; SCHOOL = school phobia; SeA = separation anxiety; SENS = sensibility; SOMAT = somatic/physical symptoms; SoA = social anxiety; SPAI-C = Social Phobia and Anxiety Inventory for Children; SPEC = specificity; STAI-C = State-Trait Anxiety Inventory for Children; T = teacher as informant; TR = test-retest; TREAT = criteria to remission/response to treatment; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; YGTSS = Yale Global Tic Severity Scale.

* Instrument with published reference of translation/cross-cultural adaptation to Brazil and psychometric properties of the Brazilian version; -- Information not available or restricted to the instrument's manual.

Regarding tricyclic antidepressants (TADs), one placebo-controlled study supported the effectiveness of clomipramine in the treatment of OCD,[159] as did two studies in children with school refusal.[30] The magnitude of medication response can be quantified using various metrics. The so-called number-needed-to-treat (NNT) is emerging as a current standard. With this metric, estimates are that approximately four patients should be using the aforementioned drugs in the anxiety disorders treatment in order to one to achieve clinical response rates (n=14 studies/2,102 patients; medication 58.1% vs. placebo 31.5%; RR = 1.9; NNT = 4).[158] This represents a very strong, robust clinical effect, relative to other conditions. For example, the NNT in either pediatric or adult depression for most medication treatments is not half as potent. There is evidence of the decrease in all anxiety symptoms with these medications. There is no direct evidence that any of these medications offer better responses to treatment or are better tolerated.[158] However, a mixed comparison meta-analysis found that between SSRIs and venlafaxine, venlafaxine was less efficacious than fluvoxamine and paroxetine and less tolerated than fluvoxamine, paroxetine, and sertraline.[160]

Besides the SSRIs and venlafaxine, three studies about the use of imipramine among patients with anxiety disorders have demonstrated its effectiveness in non-OCD disorders.[161] However, TADs are considered secondary choices due to their less favorable adverse effects and the fact that they require continuous monitoring of blood and cardiac irregularities.[158] There is no evidence supporting the use of benzodiazepines in the treatment of pediatric anxiety disorders.[162]

It is vital to emphasize that psychoeducation is an essential part of the treatment of anxiety disorders. Psychoeducation includes the explanation of the characteristics of the symptoms, course, treatment strategies, potential side effects, duration of treatment, etc. Moreover, it is critical to verify that the patient is using the medication adequately. More frequent visits in the beginning of the treatment (weekly, fortnightly) or a phone-based follow-up are good alternatives to ensure and increase treatment compliance. An algorithm to choose among the therapeutic options is depicted in Figure 3. The most used first-line medications in the treatment of anxiety disorders, their usage, and adverse effects are shown in Table 3.

Psychotherapy

CBT is the approach with stronger evidence of effectiveness as compared to waiting lists or attention control interventions for both OCD[163-165] and non-OCD pediatric anxiety disorders.[164-166] The overall effect size of CBT for pediatric anxiety in a meta-analysis involving 48 studies (n=3,740) was 0.66 (compared to passive control 0.77 and to active control 0.39; both significant), demonstrating a key role of non-specific factors.[164] The effect size for non-CBT interventions was not significant.[164] Treatment target CBT (specific to one anxiety disorder) and individual treatments (as opposed to groups) had a larger effect size than treatment targeting several anxiety disorders and group CBT.[164] Clinical trials have also shown that CBT may have better results for treating OCD when family members are involved to reduce the levels of family accommodation (the different ways that family members may respond to the patient's symptoms by facilitating avoidance, assisting on ritualistic behaviors, or inadvertently participating in rituals).[167]

Combined treatment

Two large studies have evaluated the combined treatment as compared to the monotherapy and placebo components.[108,168] For non-OCD anxiety disorders, the CBT+sertraline combined treatment was more effective than both monotherapy conditions and the placebo condition.[108] For OCD, the combined treatment was more effective than the sertraline monotherapy and the placebo conditions, but there was no difference between the combined treatment and the CBT monotherapy.[168] Data from this study investigating moderator factors of these therapy conditions have demonstrated that, for patients with a family history of OCD, the combined treatment or the sertraline monotherapy condition are preferable.[169] Conversely, for patients with comorbid OCD and tic disorders - a frequent comorbidity -, the combined treatment or the CBT are preferable.[170] Moreover, in these cases, the combination of SSRI and alpha-adrenergic agonists or anti-psychotics might be an option.[171]

Other treatments and future perspectives

Innovative treatments for anxiety disorders have been developed from the neuroscience field, such as the d-cycloserine combined with behavioral techniques[172] and the attentional bias modification treatment.[173,174] Regulators of glutamatergic neurotransmission, such as riluzole[175] and N-acetylcysteine,[176] have also been examined in adolescents diagnosed with OCD. Although promising, these treatments do not yet present long-term outcomes and are currently restricted to research settings.

Studies in adults and children have demonstrated that interventions focusing on the individual's lifestyle, such as physical exercise, are associated with improvements in anxiety and depressive symptoms,[177-179] and exercise should be encouraged. Evidence from studies with adult samples have also stated that complementary treatments with kava,[180] valerian,[181] passiflora,[182] meditation,[183] or healing touch[184] have inconclusive benefits in the treatment of anxiety disorders, with not enough evidence to recommend their use.

Monitoring, refractoriness, referring

Due to the unfavorable natural history of anxiety disorders, it is highly important to monitor anxiety symptoms and potential side effects objectively and systematically.[185] Some studies have suggested that SSRI treatments might lead to an increase in suicidality among children. Further

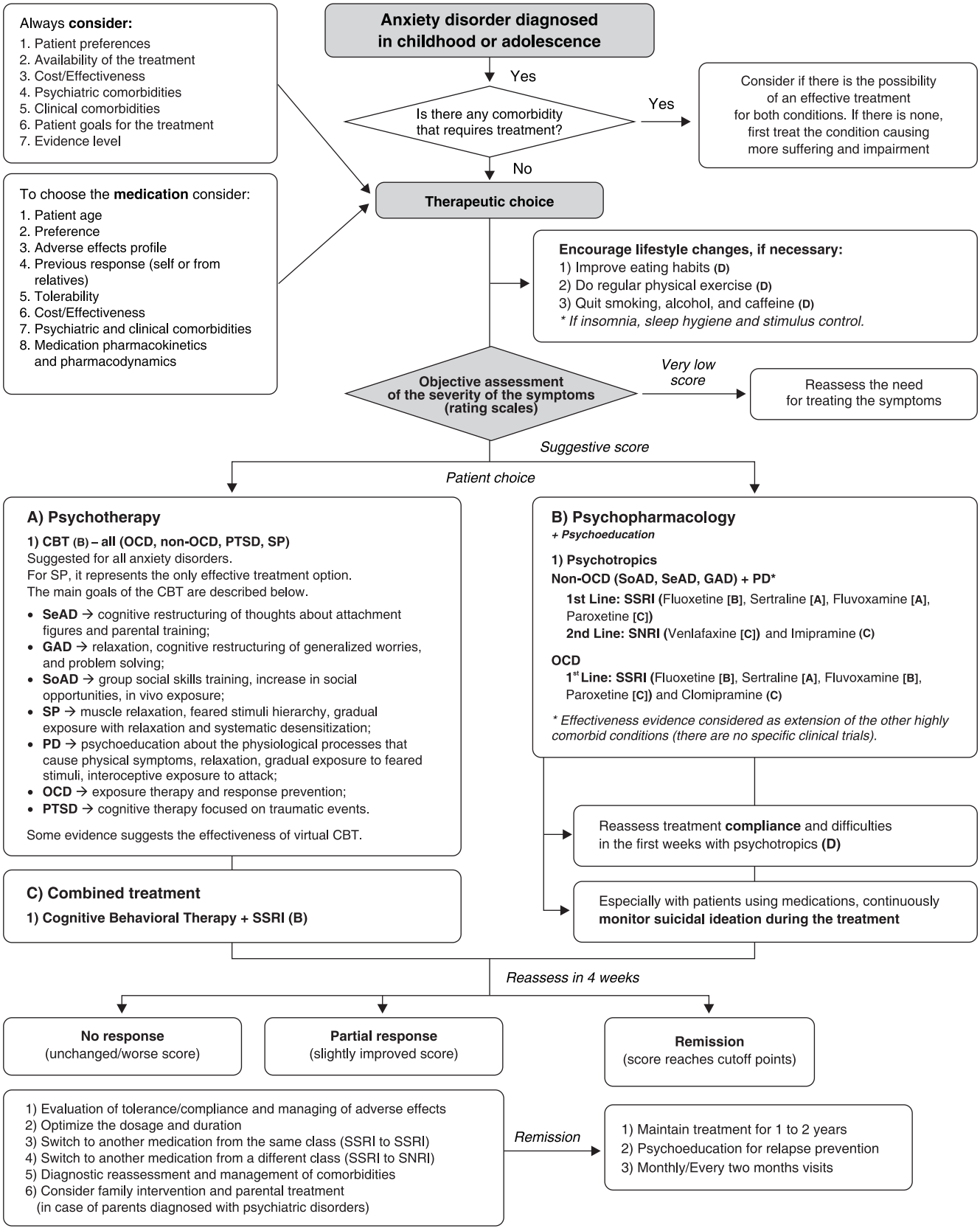

Figure 3 Algorithm for the management of pediatric anxiety disorders (based on Salum et al.[107]). CBT = cognitive behavioral therapy; GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder; PD = panic disorder; PTSD = posttraumatic stress disorder; SeAD = separation anxiety disorder; SoAD = social anxiety disorder; SP = specific phobias; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

Table 3 Main drugs used in the treatment of pediatric anxiety disorders

Drug (GRADE)	Drug use recommendations Child/Adolesc < 12 years OR Adolesc ⩾ 12 years with low weight	Drug use recommendations Adolesc with normal weight OR Children with OCD	Main characteristics (advantages/ disadvantages)
SSRI	Indications: non-OCD anxiety disorders (GAD, SoAD, SeAD) + PD and OCD Contra-indications: MAOI use, pimozide use, hypersensitivity to the drug Most common adverse effects of the class: nausea, headache, drowsiness, insomnia, dizziness, decreased appetite, abdominal pain, nervousness, excessive sweating, dry mouth, tremor, decreased sexual desire, delayed ejaculation, anorgasmia, restlessness, asthenia, abnormal platelet aggregation, and bleeding.		
Fluoxetine (B) Pills: 10 and 20 mg Oral solution: 20 mg/mL	Recommendation: start with a single dose of 5 mg/day in the morning meal for 1 week, increase to 10 mg/day and wait for therapeutic response (4-6 weeks), with increases in dose (+5 mg/day each week) according to clinical response and tolerance until the maximum dose of 20-30 mg/day, according to age and weight.	Recommendation: start with a single dose of 10 mg/day in the morning meal for 1 week, increase to 20 mg/day and wait for therapeutic response (4-6 weeks), with increases in dose (+10 mg/day each week) according to clinical response and tolerance until the maximum dose of 40-60 mg/day, according to age and weight.	- Complex metabolization (inhibits p450 CYP2D6 and CYP3A4) - Among SSRIs, it is the longest HL (HL = 4-6 days; metabolite = 4-16 days) - Among SSRIs, it is the most stimulant - Ingestion with food reduces nausea - Approved by the FDA for depression and OCD in children
Fluvoxamine (A) Pills: 100 mg	Recommendation: start with a single dose of 25 mg/day at night meals (no chewing), increase to 50 mg/day and wait for therapeutic response (4-6 weeks), with increases in dose (+25 mg/day each week) according to clinical response and tolerance until the maximum of 200 mg/day, according to age and weight. If a dosage higher than 50 mg/day is necessary, the daily dose should be divided in two (larger part at night).	Recommendation: start with a single dose of 50 mg/day at night, increase to 100 mg/day and wait for therapeutic response (4-6 weeks), with increases in dose (+50 mg/day each week) according to clinical response and tolerance until the maximum dose of 300 mg/day, according to age and weight. If a dosage higher than 100 mg/day is necessary, the daily dose should be divided in two, with the larger part at night.	- Drug absorption increases when ingested with food (but it should not be chewed) - Short HL =15 hours (in higher dosage, it must be used in two daily doses). - It presents a relative probability of causing withdrawal syndrome
Paroxetine (C) Pills: 10, 20, and 30 mg	Recommendation: start with a single dose of 5 mg/day in the morning for 1 week, increase to 10 mg/day and wait for therapeutic response (4-6 weeks), with increases in dose (+5 mg/day each week) according to clinical response and tolerance until the maximum dose of 50-60 mg/day, according to age and weight.	Recommendation: start with a single dose of 10 mg/day in the morning for 1 week, increase to 20 mg/day and wait for therapeutic response (4-6 weeks), with increases in dose (+5 mg/day each week) according to clinical response and tolerance until the maximum dose of 40-60 mg/day, according to age and weight.	- Complex metabolization (substantially inhibits p450 [CYP2D6]) - Among SSRIs, it is the less stimulant and the most sedative - Among SSRIs, it is the one with more anticholinergic effects - Short HL = 21 hours (withdrawal syndrome)
Sertraline (A) Pills: 25, 50, and 100 mg	Recommendation: start with a single dose of 12.5 mg/day in the morning meal for 1-2 weeks, increase to 25 mg/day and wait for therapeutic response (4-6 weeks), with increases in dose (+12.5 mg/day each week) according to clinical response and tolerance until the maximum dose of 200 mg/day, according to age and weight.	Recommendation: start with a single dose of 25 mg/day in the morning meal for 1-2 weeks, increase to 50 mg/day and wait for therapeutic response (4-6 weeks), with increases in dose (+25 mg/day each week) according to clinical response and tolerance until the maximum dose of 200 mg/day, according to age and weight.	- Few drug interactions (few effects p450 [CYP2D6] and minimum effects p450 [CYP3A4]) - Among SSRIs, it is the one that most causes nausea - It can be stimulant - Drug absorption increases when ingested with food - Average HL = 26 hours (+metabolite 64-104 hours)
SNRI	Indications: non-OCD anxiety disorders (GAD, SoAD, SeAD) Contraindications: hypersensitivity to MAOI Most common adverse effects: weight loss, nausea, insomnia, tremor, sexual dysfunction, sweating, dry mouth, bleeding, high blood pressure.		
Venlafaxine IR (D) (immediate release) Venlafaxine XR (C) (extended release) Pills: 37.5, 75, and 150 mg	Recommendation: start with a dose of 37.5 mg/day for 1-2 weeks, increase to 75 mg/day and wait for therapeutic response (4-6 weeks), with increases in dose (+37.5 mg/day each week) according to clinical response and tolerance until the maximum dose of 112.5 mg/day, according to age and weight. Immediate release: 2 daily doses. Extended release: single dose (in the morning).	Recommendation: start with a dose of 37.5 mg/day for 1 week, increase to 75 mg/day and wait for therapeutic response (4-6 weeks), with increases in dose (+37.5 mg/day each week) according to clinical response and tolerance until the maximum dose of 225 mg/day, according to age and weight. Immediate release: 2 daily doses. Extended release: single dose (in the morning).	- Minimum effects p450 - Frequent withdrawal syndrome Increase in arterial pressure (when dosage is higher than 225 mg) - It is important to monitor growth and weight loss - There is no evidence of effectiveness in pediatric OCD - Extended release (XR) drugs cannot be divided

Based on Salum et al.[107]
FDA = Food and Drug Administration; GAD = generalized anxiety disorder; HL = half lifetime; MAOI = monoamine oxidase inhibitors; OCD = obsessive-compulsive disorder; PD = panic disorder; SeAD = separation anxiety disorder; SNRI = serotonin and norepinephrine reuptake inhibitor; SoAD = social anxiety disorder; SSRIs = selective serotonin reuptake inhibitors.
References: UpToDate Online Pediatric Drug Information (http://www.uptodate.com). Evidence was evaluated through the GRADE quality system (A = high; B = moderate; C = low; D = very low).

studies have demonstrated that the benefits of treating anxiety disorders largely outweigh the potential risks related to the increase of suicidal ideation, which, although serious, is a rare event in the treatment of patients with anxiety disorders.[186] Nevertheless we underscore the need to monitor continuously suicidal thoughts and suicidal behaviors in this population.

There is a lack of consistent evidence regarding the best way to deal with refractory anxiety disorders or the best sequence of treatments to be applied. Overall, the recommendation is to optimize the medication dosage, since some patients only respond at higher doses (e.g., slow metabolizers, OCD patients). If there is no response after 4 to 6 weeks of treatment and after the dosage optimization, it is possible to: 1) change medications within the same class (e.g., fluoxetine for sertraline) or 2) change the previous medication for another one from a different class (e.g., fluoxetine for venlafaxine).[187]

In public health systems, specialized treatment is recommended in cases in which: 1) patients have shown refractoriness to two previous therapeutic alternatives; 2) patients have severe chronic disorders, including high level of impairment, unusually frequent avoidance behaviors and agoraphobia that do not respond to psychotropic and clearly require behavioral therapy or CBT; and 3) patients present persistent suicidal ideation.

Preschool children treatment and prevention

Most of the currently available evidence regarding the treatment of pediatric anxiety disorders is based on studies with school-aged children. However, there is a current trend to offer treatment for younger children (preschoolers), hoping that earlier diagnoses may prevent later psychiatric disorders. Parental training with CBT protocols and the treatment of mood and anxiety disorders in clinically-ill parents are suggested by some authors.[188] Although scarce, there is promising evidence that treatments based on existing therapies (CBT, parental training, and pharmacotherapy), adapted to at-risk populations, i.e., highly symptomatic children, but still not meeting criteria for the diagnosis of anxiety disorders, or children with first-degree relatives diagnosed with anxiety disorders, result in preventing and reducing the severity of these disorders.[189]

This is a general overview about pediatric anxiety disorders. More specific and comprehensive reviews about the following topics can be found in the literature: prevalence,[15,18-20] behavioral inhibition,[190-192] behavioral genetics,[48,52] genetics,[55,56,193,194] gene vs. environment interplay,[52,70] pathophysiology,[31,71] neural substrates,[71] normal development of fears,[195] psychopharmacological treatment,[196-198] and CBT.[164,199-201]

Conclusions

Anxiety disorders are prevalent, associated with a number of negative life outcomes, and currently under-recognized and under-treated. The etiology involves both genes and environmental factors in a complex interplay. Pathophysiology is still in its infancy, but some brain regions such as the amygdala and the prefrontal cortex potentially play a key role to explain individual differences related to fear and anxiety. The diagnosis is clinical and involves clinical interviews with the child, parents, and teachers. Treatment is effective using medication, CBT, or a combination of strategies.

Disclosure

Giovanni Abrahão Salum receives a post-doctoral fellowship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS). Diogo Araújo DeSouza receives a doctoral fellowship from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). Maria Conceição do Rosário receives research support from Brazilian government institutions (CNPq) and has worked in the last 5 years as a speaker for the companies Novartis and Shire. Daniel Pine declares no potential conflicts of interest. Gisele Gus Manfro receives research support from Brazilian government institutions (CNPq, FAPERGS and Fundo de Incentivo à Pesquisa - Hospital de Clínicas de Porto Alegre - FIPE-HCPA).

References

1 Woodward LJ, Fergusson DM. Life course outcomes of young people with anxiety disorders in adolescence. J Am Acad Child Adolesc Psychiatry. 2001;40:1086-93.
2 Essau CA, Conradt J, Petermann F. Frequency, comorbidity, and psychosocial impairment of anxiety disorders in German adolescents. J Anxiety Disord. 2000;14:263-79.
3 Ezpeleta L, Keeler G, Erkanli A, Costello EJ, Angold A. Epidemiology of psychiatric disability in childhood and adolescence. J Child Psychol Psychiatry. 2001;42:901-14.
4 Balázs J, Miklósi M, Keresztény A, Hoven CW, Carli V, Wasserman C, et al. Adolescent subthreshold-depression and anxiety: psychopathology, functional impairment and increased suicide risk. J Child Psychol Psychiatry. 2013;54:670-7.
5 Last CG, Hansen C, Franco N. Anxious children in adulthood: a prospective study of adjustment. J Am Acad Child Adolesc Psychiatry. 1997;36:645-52.
6 Olatunji BO, Cisler JM, Tolin DF. Quality of life in the anxiety disorders: a meta-analytic review. Clin Psychol Rev. 2007;27:572-81.
7 Nock MK, Hwang I, Sampson NA, Kessler RC. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. Mol Psychiatry. 2010;15:868-76.
8 Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol. 2010;56:38-46.
9 Baldwin DS, Pallanti S, Zwanzger P. Developing a European research network to address unmet needs in anxiety disorders. Neurosci Biobehav Rev. 2013 Jan 10. [Epub ahead of print]
10 Ranta K, Kaltiala-Heino R, Rantanen P, Marttunen M. Social phobia in Finnish general adolescent population: prevalence, comorbidity, individual and family correlates, and service use. Depress Anxiety. 2009;26:528-36.
11 Merikangas KR, He JP, Brody D, Fisher PW, Bourdon K, Koretz DS. Prevalence and treatment of mental disorders among US children in the 2001-2004 NHANES. Pediatrics. 2010;125:75-81.
12 Chavira DA, Stein MB, Bailey K, Stein MT. Child anxiety in primary care: prevalent but untreated. Depress Anxiety. 2004;20:155-64.
13 Wren FJ, Scholle SH, Heo J, Comer DM. Pediatric mood and anxiety syndromes in primary care: who gets identified? Int J Psychiatry Med. 2003;33:1-16.

14 Rutter M. Research review: child psychiatric diagnosis and classification: concepts, findings, challenges and potential. J Child Psychol Psychiatry. 2011;52:647-60.
15 Beesdo-Baum K, Knappe S. Developmental epidemiology of anxiety disorders. Child Adolesc Psychiatr Clin N Am. 2012;21:457-78.
16 Merikangas KR, He JP, Burstein M, Swanson SA, Avenevoli S, Cui L, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication--Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry. 2010;49:980-9.
17 Rapee RM, Schniering CA, Hudson JL. Anxiety disorders during childhood and adolescence: origins and treatment. Annu Rev Clin Psychol. 2009;5:311-41.
18 Costello EJ, Egger HL, Angold A. The developmental epidemiology of anxiety disorders: phenomenology, prevalence, and comorbidity. Child Adolesc Psychiatr Clin N Am. 2005;14:631-48.
19 Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. Psychiatr Clin North Am. 2009;32:483-524.
20 Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychol Med. 2013;43:897-910.
21 Somers JM, Goldner EM, Waraich P, Hsu L. Prevalence and incidence studies of anxiety disorders: a systematic review of the literature. Can J Psychiatry. 2006;51:100-13.
22 Adornetto C, Suppiger A, In-Albon T, Neuschwander M, Schneider S. Concordances and discrepancies between ICD-10 and DSM-IV criteria for anxiety disorders in childhood and adolescence. Child Adolesc Psychiatry Ment Health. 2012;6:40.
23 Salum GA, Isolan LR, Bosa VL, Tocchetto AG, Teche SP, Schuch I, et al. The multidimensional evaluation and treatment of anxiety in children and adolescents: rationale, design, methods and preliminary findings. Rev Bras Psiquiatr. 2011;33:181-95.
24 Baxter AJ, Charlson FJ, Somerville AJ, Whiteford HA. Mental disorders as risk factors: assessing the evidence for the Global Burden of Disease Study. BMC Med. 2011;9:134.
25 Anselmi L, Fleitlich-Bilyk B, Menezes AM, Araujo CL, Rohde LA. Prevalence of psychiatric disorders in a Brazilian birth cohort of 11-year-olds. Soc Psychiatry Psychiatr Epidemiol. 2010;45:135-42.
26 Fleitlich-Bilyk B, Goodman R. Prevalence of child and adolescent psychiatric disorders in southeast Brazil. J Am Acad Child Adolesc Psychiatry. 2004;43:727-34.
27 Craske MG. Origins of phobias and anxiety disorders: why more women than men? Amsterdam: Elsevier; 2003.
28 American Psychiatric Association. Diagnostic and statistical manual of mental disorders - DSM-IV-TR®. 4th ed. Arlington: American Psychiatric Publishing; 1994.
29 Gregory AM, Caspi A, Moffitt TE, Koenen K, Eley TC, Poulton R. Juvenile mental health histories of adults with anxiety disorders. Am J Psychiatry. 2007;164:301-8.
30 Pine DS, Klein RG. Anxiety disorders. In: Rutter M, Bishop DVM, Pine DS, Scott S, Stevenson J, Taylor E, Thapar A , editors. Rutter's child and adolescent psychiatry. 5th ed. Oxford: Blackwell Publishing Ltd; 2009. p. 628-647.
31 Pine DS. Research review: a neuroscience framework for pediatric anxiety disorders. J Child Psychol Psychiatry. 2007;48:631-48.
32 Wittchen HU, Lieb R, Pfister H, Schuster P. The waxing and waning of mental disorders: evaluating the stability of syndromes of mental disorders in the population. Compr Psychiatry. 2000;41:122-32.
33 Kessler RC, Avenevoli S, Costello EJ, Georgiades K, Green JG, Gruber MJ, et al. Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. Arch Gen Psychiatry. 2012;69:372-80.
34 Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Arch Gen Psychiatry. 1998;55:56-64.
35 Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. Arch Gen Psychiatry. 2009;66:764-72.
36 Bittner A, Egger HL, Erkanli A, Jane Costello E, Foley DL, Angold A. What do childhood anxiety disorders predict? J Child Psychol Psychiatry. 2007;48:1174-83.
37 Angst J, Vollrath M. The natural history of anxiety disorders. Acta Psychiatr Scand. 1991;84:446-52.
38 Beesdo K, Pine DS, Lieb R, Wittchen HU. Incidence and risk patterns of anxiety and depressive disorders and categorization of generalized anxiety disorder. Arch Gen Psychiatry. 2010;67:47-57.
39 Last CG, Perrin S, Hersen M, Kazdin AE. A prospective study of childhood anxiety disorders. J Am Acad Child Adolesc Psychiatry. 1996;35:1502-10.
40 Pine DS, Cohen P, Brook J. Adolescent fears as predictors of depression. Biol Psychiatry. 2001;50:721-4.
41 Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch Gen Psychiatry. 2003;60:709-17.
42 Colman I, Wadsworth ME, Croudace TJ, Jones PB. Forty-year psychiatric outcomes following assessment for internalizing disorder in adolescence. Am J Psychiatry. 2007;164:126-33.
43 Scholten WD, Batelaan NM, van Balkom AJ, Wjh Penninx B, Smit JH, van Oppen P. Recurrence of anxiety disorders and its predictors. J Affect Disord. 2013;147:180-5.
44 Insel TR. Disruptive insights in psychiatry: transforming a clinical discipline. J Clin Invest. 2009;119:700-5.
45 Insel TR, Quirion R. Psychiatry as a clinical neuroscience discipline. JAMA. 2005;294:2221-4.
46 Levitt P, March J. NIMH Council Workgroup on Neurodevelopment: Update on Activities and Workgroup Recommendations. Bethesda, MD: 2008.
47 Skre I, Onstad S, Edvardsen J, Torgersen S, Kringlen E. A family study of anxiety disorders: familial transmission and relationship to mood disorder and psychoactive substance use disorder. Acta Psychiatr Scand. 1994;90:366-74.
48 Gregory AM, Eley TC. Genetic influences on anxiety in children: what we've learned and where we're heading. Clin Child Family Psychol Rev. 2007;10:199-212.
49 Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. American J Psychiatry. 2001;158:1568-78.
50 Topolski TD, Hewitt JK, Eaves L, Meyer JM, Silberg JL, Simonoff E, et al. Genetic and environmental influences on ratings of manifest anxiety by parents and children. J Anxiety Disord. 1999;13:371-97.
51 Hettema JM, Prescott CA, Myers JM, Neale MC, Kendler KS. The structure of genetic and environmental risk factors for anxiety disorders in men and women. Arch Gen Psychiatry. 2005;62:182-9.
52 Franić S, Middeldorp CM, Dolan CV, Ligthart L, Boomsma DI. Childhood and adolescent anxiety and depression: beyond heritability. J Am Acad Child Adolesc Psychiatry. 2010;49:820-9.
53 Rommelse NN, Franke B, Geurts HM, Hartman CA, Buitelaar JK. Shared heritability of attention-deficit/hyperactivity disorder and autism spectrum disorder. Eur Child Adolesc Psychiatry. 2010;19:281-95.
54 Lahey BB, Van Hulle CA, Singh AL, Waldman ID, Rathouz PJ. Higher-order genetic and environmental structure of prevalent forms of child and adolescent psychopathology. Arch Gen Psychiatry. 2011;68:181-9.
55 Sakolsky DJ, McCracken JT, Nurmi EL. Genetics of pediatric anxiety disorders. Child Adolesc Psychiatr Clin N Am. 2012;21:479-500.
56 McGrath LM, Weill S, Robinson EB, Macrae R, Smoller JW. Bringing a developmental perspective to anxiety genetics. Dev Psychopathol. 2012;24:1179-93.
57 Erhardt A, Czibere L, Roeske D, Lucae S, Unschuld PG, Ripke S, et al. TMEM132D, a new candidate for anxiety phenotypes: evidence from human and mouse studies. Mol Psychiatry. 2011;16:647-63.
58 Otowa T, Tanii H, Sugaya N, Yoshida E, Inoue K, Yasuda S, et al. Replication of a genome-wide association study of panic disorder in a Japanese population. J Hum Genet. 2010;55:91-6.
59 Otowa T, Yoshida E, Sugaya N, Yasuda S, Nishimura Y, Inoue K, et al. Genome-wide association study of panic disorder in the Japanese population. J Hum Genet. 2009;54:122-6.

60 Stewart SE, Yu D, Scharf JM, Neale BM, Fagerness JA, Mathews CA, et al. Genome-wide association study of obsessive-compulsive disorder. Mol Psychiatry. 2012 Aug 14. [Epub ahead of print]

61 Logue MW, Baldwin C, Guffanti G, Melista E, Wolf EJ, Reardon AF, et al. A genome-wide association study of post-traumatic stress disorder identifies the retinoid-related orphan receptor alpha (RORA) gene as a significant risk locus. Mol Psychiatry. 2012 Aug 7. [Epub ahead of print]

62 Gregersen N, Dahl HA, Buttenschon HN, Nyegaard M, Hedemand A, Als TD, et al. A genome-wide study of panic disorder suggests the amiloride-sensitive cation channel 1 as a candidate gene. Eur J Hum Genet. 2012;20:84-90.

63 Otowa T, Kawamura Y, Nishida N, Sugaya N, Koike A, Yoshida E, et al. Meta-analysis of genome-wide association studies for panic disorder in the Japanese population. Transl Psychiatry. 2012;2:e186.

64 Kawamura Y, Otowa T, Koike A, Sugaya N, Yoshida E, Yasuda S, et al. A genome-wide CNV association study on panic disorder in a Japanese population. J Hum Genet. 2011;56:852-6.

65 Lau JY, Gregory AM, Goldwin MA, Pine DS, Eley TC. Assessing gene-environment interactions on anxiety symptom subtypes across childhood and adolescence. Dev Psychopathol. 2007;19:1129-46.

66 Hicks BM, DiRago AC, Iacono WG, McGue M. Gene-environment interplay in internalizing disorders: consistent findings across six environmental risk factors. J Child Psychol Psychiatry. 2009;50:1309-17.

67 Narusyte J, Neiderhiser JM, D'Onofrio BM, Reiss D, Spotts EL, Ganiban J, et al. Testing different types of genotype-environment correlation: an extended children-of-twins model. Dev Psychol. 2008;44:1591-603.

68 Kendler KS, Baker JH. Genetic influences on measures of the environment: a systematic review. Psychol Med. 2007;37:615-26.

69 Kendler KS. Parenting: a genetic-epidemiologic perspective. Am J Psychiatry. 1996;153:11-20.

70 Rutter M, Moffitt TE, Caspi A. Gene-environment interplay and psychopathology: multiple varieties but real effects. J Child Psychol Psychiatry. 2006;47:226-61.

71 Blackford JU, Pine DS. Neural substrates of childhood anxiety disorders: a review of neuroimaging findings. Child Adolesc Psychiatr Clin N Am. 2012;21:501-25.

72 Shechner T, Britton JC, Pérez-Edgar K, Bar-Haim Y, Ernst M, Fox NA, et al. Attention biases, anxiety, and development: toward or away from threats or rewards? Depress Anxiety. 2012;29:282-94.

73 Britton JC, Lissek S, Grillon C, Norcross MA, Pine DS. Development of anxiety: the role of threat appraisal and fear learning. Depress Anxiety. 2011;28:5-17.

74 Lissek S. Toward an account of clinical anxiety predicated on basic, neurally mapped mechanisms of Pavlovian fear-learning: the case for conditioned overgeneralization. Depress Anxiety. 2012;29: 257-63.

75 Kheirbek MA, Klemenhagen KC, Sahay A, Hen R. Neurogenesis and generalization: a new approach to stratify and treat anxiety disorders. Nat Neurosci. 2012;15:1613-20.

76 Guyer AE, Lau JY, McClure-Tone EB, Parrish J, Shiffrin ND, Reynolds RC, et al. Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. Arch Gen Psychiatry. 2008;65:1303-12.

77 Guyer AE, Choate VR, Detloff A, Benson B, Nelson EE, Perez-Edgar K, et al. Striatal functional alteration during incentive anticipation in pediatric anxiety disorders. Am J Psychiatry. 2012;169:205-12.

78 Guyer AE, Nelson EE, Perez-Edgar K, Hardin MG, Roberson-Nay R, Monk CS, et al. Striatal functional alteration in adolescents characterized by early childhood behavioral inhibition. J Neurosci. 2006;26:6399-405.

79 Mana S, Paillère Martinot ML, Martinot JL. Brain imaging findings in children and adolescents with mental disorders: a cross-sectional review. Eur Psychiatry. 2010;25:345-54.

80 Milad MR, Rauch SL. Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. Trends Cogn Sci. 2012;16: 43-51.

81 Rapee RM. Potential role of childrearing practices in the development of anxiety and depression. Clin Psychol Rev. 1997;17:47-67.

82 McLeod BD, Wood JJ, Weisz JR. Examining the association between parenting and childhood anxiety: a meta-analysis. Clin Psychol Rev. 2007;27:155-72.

83 Allen JL, Rapee RM, Sandberg S. Severe life events and chronic adversities as antecedents to anxiety in children: a matched control study. J Abnorm Child Psychol. 2008;36:1047-56.

84 Eley TC, Stevenson J. Specific life events and chronic experiences differentially associated with depression and anxiety in young twins. J Abnorm Child Psychol. 2000;28:383-94.

85 Murray L, Creswell C, Cooper PJ. The development of anxiety disorders in childhood: an integrative review. Psychol Med. 2009;39:1413-23.

86 Otowa T, Gardner CO, Kendler KS, Hettema JM. Parenting and risk for mood, anxiety and substance use disorders: a study in population-based male twins. Soc Psychiatry Psychiatr Epidemiol. 2013 Jan 24. [Epub ahead of print]

87 de Rosnay M, Cooper PJ, Tsigaras N, Murray L. Transmission of social anxiety from mother to infant: an experimental study using a social referencing paradigm. Behav Res Ther. 2006;44:1165-75.

88 Gerull FC, Rapee RM. Mother knows best: effects of maternal modelling on the acquisition of fear and avoidance behaviour in toddlers. Behav Res Ther. 2002;40:279-87.

89 Murray L, de Rosnay M, Pearson J, Bergeron C, Schofield E, Royal-Lawson M, et al. Intergenerational transmission of social anxiety: the role of social referencing processes in infancy. Child Dev. 2008;79:1049-64.

90 Field AP. Is conditioning a useful framework for understanding the development and treatment of phobias? Clin Psychol Rev. 2006;26:857-75.

91 Field AP, Lawson J. Fear information and the development of fears during childhood: effects on implicit fear responses and behavioural avoidance. Behav Res Ther. 2003;41:1277-93.

92 Kraemer HC, Kazdin AE, Offord DR, Kessler RC, Jensen PS, Kupfer DJ. Coming to terms with the terms of risk. Arch Gen Psychiatry. 1997;54:337-43.

93 Kraemer HC, Stice E, Kazdin A, Offord D, Kupfer D. How do risk factors work together? Mediators, moderators, and independent, overlapping, and proxy risk factors. Am J Psychiatry. 2001;158: 848-56.

94 Kendler KS. "A gene for...": the nature of gene action in psychiatric disorders. Am J Psychiatry. 2005;162:1243-52.

95 Kendler KS. Preparing for gene discovery: a further agenda for psychiatry. Arch Gen Psychiatry. 1999;56:554-5.

96 Kendler KS. Explanatory models for psychiatric illness. Am J Psychiatry. 2008;165:695-702.

97 Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010;167:748-51.

98 Sanislow CA, Pine DS, Quinn KJ, Kozak MJ, Garvey MA, Heinssen RK, et al. Developing constructs for psychopathology research: research domain criteria. J Abnorm Psychol. 2010;119:631-9.

99 Coghill D, Sonuga-Barke EJ. Annual research review: categories versus dimensions in the classification and conceptualisation of child and adolescent mental disorders--implications of recent empirical study. J Child Psychol Psychiatry. 2012;53:469-89.

100 Skarin K. Cognitive and contextual determinants of stranger fear in six- and eleven-month-old infants. Child Dev. 1977;48:537-44.

101 Thompson RA, Limber SP. "Social anxiety" in infancy: stranger and separation reactions. In: Leitenberg H, editor. Handbook of social and evaluation anxiety. New York: Plenum Press; 1990. p. 85-137.

102 Kagan J, Snidman N, Zentner M, Peterson E. Infant temperament and anxious symptoms in school age children. Dev Psychopathol. 1999;11:209-24.

103 Clauss JA, Blackford JU. Behavioral inhibition and risk for developing social anxiety disorder: a meta-analytic study. J Am Acad Child Adolesc Psychiatry. 2012;51:1066-75.

104 Degnan KA, Almas AN, Fox NA. Temperament and the environment in the etiology of childhood anxiety. J Child Psychol Psychiatry. 2010;51:497-517.

105 Noel VA, Francis SE. A meta-analytic review of the role of child anxiety sensitivity in child anxiety. J Abnorm Child Psychol. 2011;39:721-33.

106 Olatunji BO, Wolitzky-Taylor KB. Anxiety sensitivity and the anxiety disorders: a meta-analytic review and synthesis. Psychol Bull. 2009;135:974-99.
107 Salum GA, Alvarenga PG, Manfro GG. Transtornos de ansiedade e transtorno obsessivo-compulsivo. In: Polanczyk GV, Lamberte MTMR, editors. Psiquiatria da infância e adolescência. São Paulo: Manole; 2012.
108 Walkup JT, Albano AM, Piacentini J, Birmaher B, Compton SN, Sherrill JT, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. N Engl J Med. 2008;359:2753-66.
109 Angold A, Costello EJ, Erkanli A. Comorbidity. J Child Psychol Psychiatry. 1999;40:57-87.
110 Wolitzky-Taylor K, Bobova L, Zinbarg RE, Mineka S, Craske MG. Longitudinal investigation of the impact of anxiety and mood disorders in adolescence on subsequent substance use disorder onset and vice versa. Addict Behav. 2012;37:982-5.
111 Moffitt TE, Harrington H, Caspi A, Kim-Cohen J, Goldberg D, Gregory AM, et al. Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. Arch Gen Psychiatry. 2007;64:651-60.
112 Gandhi B, Cheek S, Campo JV. Anxiety in the pediatric medical setting. Child Adolesc Psychiatr Clin N Am. 2012;21:643-53.
113 Brasil HHA. Development of the Brazilian version of K-SADS-PL (Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version) and study of psychometric properties [dissertation]. São Paulo: Universidade Federal de São Paulo; 2003.
114 Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997;36:980-8.
115 Polanczyk GV, Eizirik M, Aranovich V, Denardin D, da Silva TL, da Conceicao TV, et al. Interrater agreement for the schedule for affective disorders and schizophrenia epidemiological version for school-age children (K-SADS-E). Rev Bras Psiquiatr. 2003;25:87-90.
116 Angold A, Erkanli A, Copeland W, Goodman R, Fisher PW, Costello EJ. Psychiatric diagnostic interviews for children and adolescents: a comparative study. J Am Acad Child Adolesc Psychiatry. 2012;51:506-17.
117 Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. J Child Psychol Psychiatry. 2000;41:645-55.
118 Souza IGS, Serra-Pinheiro MA, Mousinho R, Mattos PA. A Brazilian version of the ''Children's Interview for Psychiatric Syndromes'' (ChIPS). J Bras Psiquiatr. 2009;58:115-8.
119 Weller EB, Weller RA, Fristad MA, Rooney MT, Schecter J. Children's Interview for Psychiatric Syndromes (ChIPS). J Am Acad Child Adolesc Psychiatry. 2000;39:76-84.
120 Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. J Am Acad Child Adolesc Psychiatry. 2000;39:28-38.
121 Reich W. Diagnostic interview for children and adolescents (DICA). J Am Acad Child Adolesc Psychiatry. 2000;39:59-66.
122 Welner Z, Reich W, Herjanic B, Jung KG, Amado H. Reliability, validity, and parent-child agreement studies of the Diagnostic Interview for Children and Adolescents (DICA). J Am Acad Child Adolesc Psychiatry. 1987;26:649-53.
123 Sherrill JT, Kovacs M. Interview schedule for children and adolescents (ISCA). J Am Acad Child Adolesc Psychiatry. 2000;39:67-75.
124 Lyneham HJ, Abbott MJ, Rapee RM. Interrater reliability of the Anxiety Disorders Interview Schedule for DSM-IV: child and parent version. J Am Acad Child Adolesc Psychiatry. 2007;46:731-6.
125 Silverman WK, Saavedra LM, Pina AA. Test-retest reliability of anxiety symptoms and diagnoses with the Anxiety Disorders Interview Schedule for DSM-IV: child and parent versions. J Am Acad Child Adolesc Psychiatry. 2001;40:937-44.
126 Angold A, Costello EJ. The Child and Adolescent Psychiatric Assessment (CAPA). J Am Acad Child Adolesc Psychiatry. 2000;39:39-48.
127 Angold A, Prendergast M, Cox A, Harrington R, Simonoff E, Rutter M. The Child and Adolescent Psychiatric Assessment (CAPA). Psychol Med. 1995;25:739-53.
128 Egger HL, Erkanli A, Keeler G, Potts E, Walter BK, Angold A. Test-retest reliability of the Preschool Age Psychiatric Assessment (PAPA). J Am Acad Child Adolesc Psychiatry. 2006;45:538-49.
129 Merikangas K, Avenevoli S, Costello J, Koretz D, Kessler RC. National comorbidity survey replication adolescent supplement (NCS-A): I. background and measures. J Am Acad Child Adolesc Psychiatry. 2009;48:367-9.
130 Biaggio AMB, Spielberger CD. [Manual of the Portuguese form of the STAI]. Rio de Janeiro: CEPA; 1983.
131 Spielberger CD. Manual for the State-Trait Anxiety Inventory for Children. Palo Alto: Consulting Psychologist Press; 1973.
132 Gorayeb MAM, Gorayeb R. [Revised Children's Manifest Anxiety Scale (RCMAS) adapt to Portuguese in Brazil]. Temas Psicol. 2008;16:35-45.
133 Reynolds CR, Richmond BO. What I think and feel: a revised measure of children's manifest anxiety. J Abnorm Child Psychol. 1997;25:15-20.
134 Beck JS, Beck AT, Jolly JB, Steer RA. Beck Youth Inventories for children and adolescents: manual. 2nd ed. San Antonio: Harcourt Assessment, Inc; 2005.
135 The Pediatric Anxiety Rating Scale (PARS): development and psychometric properties. J Am Acad Child Adolesc Psychiatry. 2002;41:1061-9.
136 Caporino NE, Brodman DM, Kendall PC, Albano AM, Sherrill J, Piacentini J, et al. Defining treatment response and remission in child anxiety: signal detection analysis using the pediatric anxiety rating scale. J Am Acad Child Adolesc Psychiatry. 2013;52:57-67.
137 Birmaher B, Brent DA, Chiappetta L, Bridge J, Monga S, Baugher M. Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. J Am Acad Child Adolesc Psychiatry. 1999;38:1230-6.
138 Birmaher B, Khetarpal S, Brent D, Cully M, Balach L, Kaufman J, et al. The Screen for Child Anxiety Related Emotional Disorders (SCARED): scale construction and psychometric characteristics. J Am Acad Child Adolesc Psychiatry. 1997;36:545-53.
139 Desousa DA, Salum GA, Isolan LR, Manfro GG. Sensitivity and specificity of the screen for Child Anxiety Related Emotional Disorders (SCARED): a community-based study. Child Psychiatry Hum Dev. 2013;44:391-9.
140 Isolan L, Salum GA, Osowski AT, Amaro E, Manfro GG. Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED) in Brazilian children and adolescents. J Anxiety Disord. 2011;25:741-8.
141 DeSousa DA, Petersen CS, Behs R, Manfro GG, Koller SH. Brazilian Portuguese version of the Spence Children's Anxiety Scale (SCAS-Brasil). Trends Psychiatry Psychother. 2012;34:147-53.
142 Spence SH. A measure of anxiety symptoms among children. Behav Res Ther. 1998;36:545-66.
143 Spence SH. Structure of anxiety symptoms among children: a confirmatory factor-analytic study. J Abnorm Psychol. 1997;106:280-97.
144 March JS, Parker JD, Sullivan K, Stallings P, Conners CK. The Multidimensional Anxiety Scale for Children (MASC): factor structure, reliability, and validity. J Am Acad Child Adolesc Psychiatry. 1997;36:554-65.
145 Masia-Warner C, Storch EA, Pincus DB, Klein RG, Heimberg RG, Liebowitz MR. The Liebowitz social anxiety scale for children and adolescents: an initial psychometric investigation. J Am Acad Child Adolesc Psychiatry. 2003;42:1076-84.
146 Gauer GC, Picon P, Davoglio TR, Silva LM, Beidel DC. Psychometric characteristics of the Brazilian Portuguese version of Social Phobia and Anxiety Inventory for Children (SPAI-C). Psico. 2009;40:354-8.
147 Gauer GJ, Picon P, Vasconcellos SJ, Turner SM, Beidel DC. Validation of the Social Phobia and Anxiety Inventory for Children (SPAI-C) in a sample of Brazilian children. Braz J Med Biol Res. 2005;38:795-800.

148 Scaini S, Battaglia M, Beidel DC, Ogliari A. A meta-analysis of the cross-cultural psychometric properties of the Social Phobia and Anxiety Inventory for Children (SPAI-C). J Anxiety Disord. 2012:182-8.
149 Beidel DC, Turner SM, Morris TL. A new inventory to assess childhood social anxiety and phobia: The Social Phobia and Anxiety Inventory for Children. Psychol Assess. 1995;7:73-9.
150 Freeman J, Flessner CA, Garcia A. The Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity for use among 5 to 8 year olds with obsessive-compulsive disorder. J Abnorm Child Psychol. 2011;39:877-83.
151 Scahill L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, Goodman WK, et al. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. J Am Acad Child Adolesc Psychiatry. 1997;36:844-52.
152 Storch EA, Murphy TK, Adkins JW, Lewin AB, Geffken GR, Johns NB, et al. The children's Yale-Brown obsessive-compulsive scale: psychometric properties of child- and parent-report formats. J Anxiety Disord. 2006;20:1055-70.
153 Rosario-Campos MC, Miguel EC, Quatrano S, Chacon P, Ferrao Y, Findley D, et al. The Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS): an instrument for assessing obsessive-compulsive symptom dimensions. Mol Psychiatry. 2006;11:495-504.
154 Ollendick TH. Reliability and validity of the Revised Fear Surgery Schedule for Children (FSSC-R). Behav Res Ther. 1983;21:685-92.
155 Masi G, Pari C, Millepiedi S. Pharmacological treatment options for panic disorder in children and adolescents. Expert Opin Pharmacother. 2006;7:545-54.
156 Pine DS, Cohen JA. Trauma in children and adolescents: risk and treatment of psychiatric sequelae. Biol Psychiatry. 2002;51:519-31.
157 Cohen JA, Bukstein O, Walter H, Benson SR, Chrisman A, Farchione TR, et al. Practice parameter for the assessment and treatment of children and adolescents with posttraumatic stress disorder. J Am Acad Child Adolesc Psychiatry. 2010;49:414-30.
158 Ipser JC, Stein DJ, Hawkridge S, Hoppe L. Pharmacotherapy for anxiety disorders in children and adolescents. Cochrane Database Syst Rev. 2009:CD005170.
159 DeVeaugh-Geiss J, Moroz G, Biederman J, Cantwell D, Fontaine R, Greist JH, et al. Clomipramine hydrochloride in childhood and adolescent obsessive-compulsive disorder--a multicenter trial. J Am Acad Child Adolesc Psychiatry. 1992;31:45-9.
160 Uthman OA, Abdulmalik J. Comparative efficacy and acceptability of pharmacotherapeutic agents for anxiety disorders in children and adolescents: a mixed treatment comparison meta-analysis. Curr Med Res Opin. 2010;26:53-9.
161 Connolly SD, Suarez L, Sylvester C. Assessment and treatment of anxiety disorders in children and adolescents. Curr Psychiatry Rep. 2011;13:99-110.
162 Graae F, Milner J, Rizzotto L, Klein RG. Clonazepam in childhood anxiety disorders. J Am Acad Child Adolesc Psychiatry. 1994;33:372-6.
163 O'Kearney RT, Anstey KJ, von Sanden C. Behavioural and cognitive behavioural therapy for obsessive compulsive disorder in children and adolescents. Cochrane Database Syst Rev. 2006:CD004856.
164 Reynolds S, Wilson C, Austin J, Hooper L. Effects of psychotherapy for anxiety in children and adolescents: a meta-analytic review. Clin Psychol Rev. 2012;32:251-62.
165 Davis TE, 3rd, May A, Whiting SE. Evidence-based treatment of anxiety and phobia in children and adolescents: current status and effects on the emotional response. Clin Psychol Rev. 2011;31:592-602.
166 James A, Soler A, Weatherall R. Cognitive behavioural therapy for anxiety disorders in children and adolescents. Cochrane Database Syst Rev. 2005:CD004690.
167 Alvarenga PG, Mastrorosa RS, Rosário MC. Obsessive compulsive disorder in children and adolescents. In Rey JM, editor. IACAPAP e-Textbook of Child and Adolescent Mental Health. Geneva: International Association for Child and Adolescent Psychiatry and Allied Professions; 2012. p. 1-17.
168 Pediatric OCD Treatment Study (POTS) Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. JAMA. 2004;292:1969-76.
169 Garcia AM, Sapyta JJ, Moore PS, Freeman JB, Franklin ME, March JS, et al. Predictors and moderators of treatment outcome in the Pediatric Obsessive Compulsive Treatment Study (POTS I). J Am Acad Child Adolesc Psychiatry. 2011;49:1024-33.
170 March JS, Franklin ME, Leonard H, Garcia A, Moore P, Freeman J, et al. Tics moderate treatment outcome with sertraline but not cognitive-behavior therapy in pediatric obsessive-compulsive disorder. Biol Psychiatry. 2007;61:344-7.
171 Rosário M, Alvarenga P, Mathis M, Leckman J. Obsessive-compulsive disorder in childhood. In: Banaschewski T, Rohde L, editors. Biological child psychiatry - recent trends and developments. Basel: Karger; 2008. p. 82-94.
172 Norberg MM, Krystal JH, Tolin DF. A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. Biol Psychiatry. 2008;63:1118-26.
173 Hakamata Y, Lissek S, Bar-Haim Y, Britton JC, Fox NA, Leibenluft E, et al. Attention bias modification treatment: a meta-analysis toward the establishment of novel treatment for anxiety. Biol Psychiatry. 2010;68:982-90.
174 Eldar S, Apter A, Lotan D, Edgar KP, Naim R, Fox NA, et al. Attention bias modification treatment for pediatric anxiety disorders: a randomized controlled trial. Am J Psychiatry. 2012;169:213-20.
175 Pittenger C, Kelmendi B, Wasylink S, Bloch MH, Coric V. Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: a series of 13 cases, with long-term follow-up. J Clin Psychopharmacol. 2008;28:363-7.
176 Grant JE, Kim SW, Odlaug BL. N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling: a pilot study. Biol Psychiatry. 2007;62:652-7.
177 Jayakody K, Gunadasa S, Hosker C. Exercise for anxiety disorders: systematic review. Br J Sports Med. 2013 Jan 7. [Epub ahead of print]
178 Asmundson GJ, Fetzner MG, Deboer LB, Powers MB, Otto MW, Smits JA. Let's get physical: a contemporary review of the anxiolytic effects of exercise for anxiety and its disorders. Depress Anxiety. 2013;30:362-73.
179 Larun L, Nordheim LV, Ekeland E, Hagen KB, Heian F. Exercise in prevention and treatment of anxiety and depression among children and young people. Cochrane Database Syst Rev. 2006:CD004691.
180 Pittler MH, Ernst E. Kava extract for treating anxiety. Cochrane Database Syst Rev. 2003:CD003383.
181 Miyasaka LS, Atallah AN, Soares BG. Valerian for anxiety disorders. Cochrane Database Syst Rev. 2006:CD004515.
182 Miyasaka LS, Atallah AN, Soares BG. Passiflora for anxiety disorder. Cochrane Database Syst Rev. 2007:CD004518.
183 Krisanaprakornkit T, Krisanaprakornkit W, Piyavhatkul N, Laopaiboon M. Meditation therapy for anxiety disorders. Cochrane Database Syst Rev. 2006:CD004998.
184 Robinson J, Biley FC, Dolk H. Therapeutic touch for anxiety disorders. Cochrane Database Syst Rev. 2007:CD006240.
185 Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006;163:28-40.
186 Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA. 2007;297:1683-96.
187 Stein DJ, Baldwin DS, Bandelow B, Blanco C, Fontenelle LF, Lee S, et al. A 2010 evidence-based algorithm for the pharmacotherapy of social anxiety disorder. Curr Psychiatry Rep. 2010;12:471-7.
188 Gleason MM, Egger HL, Emslie GJ, Greenhill LL, Kowatch RA, Lieberman AF, et al. Psychopharmacological treatment for very young children: contexts and guidelines. J Am Acad Child Adolesc Psychiatry. 2007;46:1532-72.
189 Rapee RM, Kennedy SJ, Ingram M, Edwards SL, Sweeney L. Altering the trajectory of anxiety in at-risk young children. Am J Psychiatry. 2010;167:1518-25.
190 Degnan KA, Fox NA. Behavioral inhibition and anxiety disorders: multiple levels of a resilience process. Dev Psychopathol. 2007;19:729-46.

191 Fox NA, Henderson HA, Marshall PJ, Nichols KE, Ghera MM. Behavioral inhibition: linking biology and behavior within a developmental framework. Annu Rev Psychol. 2005;56:235-62.
192 Hirshfeld-Becker DR, Micco J, Henin A, Bloomfield A, Biederman J, Rosenbaum J. Behavioral inhibition. Depress Anxiety. 2008;25: 357-67.
193 Smoller JW, Block SR, Young MM. Genetics of anxiety disorders: the complex road from DSM to DNA. Depress Anxiety. 2009;26:965-75.
194 Domschke K, Deckert J. Genetics of anxiety disorders - status quo and quo vadis. Curr Pharm Des. 2012;18:5691-8.
195 Gullone E. The development of normal fear: a century of research. Clin Psychol Rev. 2000;20:429-51.
196 Strawn JR, Sakolsky DJ, Rynn MA. Psychopharmacologic treatment of children and adolescents with anxiety disorders. Child Adolesc Psychiatr Clin N Am. 2012;21:527-39.
197 Rynn M, Puliafico A, Heleniak C, Rikhi P, Ghalib K, Vidair H. Advances in pharmacotherapy for pediatric anxiety disorders. Depress Anxiety. 2011;28:76-87.
198 Peters TE, Connolly S. Psychopharmacologic treatment for pediatric anxiety disorders. Child Adolesc Psychiatr Clin N Am. 2012;21:789-806.
199 Kar N. Cognitive behavioral therapy for the treatment of post-traumatic stress disorder: a review. Neuropsychiatr Dis Treat. 2011;7:167-81.
200 Kircanski K, Peris TS, Piacentini JC. Cognitive-behavioral therapy for obsessive-compulsive disorder in children and adolescents. Child Adolesc Psychiatr Clin N Am. 2011;20:239-54.
201 Seligman LD, Ollendick TH. Cognitive-behavioral therapy for anxiety disorders in youth. Child Adolesc Psychiatr Clin N Am. 2011;20:217-38.